SHL
WITHDRAWN

Dup

TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

TWENTIETH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 16 AND 17, 1905.

VOLUME XX.

PHILADELPHIA:
PRINTED FOR THE ASSOCIATION.
1905.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings

DORNAN, PRINTER,
701-709 ARCH STREET,
PHILADELPHIA.

CONTENTS.

	PAGE
List of Officers for the year 1905–1906	vii
List of Officers from organization to the present time	viii
List of Members	ix
List of Associate Members	xiii
List of Honorary Members	xv
List of Deceased Members	xvii
Constitution	xix
Minutes of the Nineteenth Annual Meeting	xxiii

PAPERS.

Address of the President. By E. L. Trudeau, M.D.	1
Of Ailurophobia and the Power to be Conscious of the Cat as Near, When Unseen and Unheard. By S. Weir Mitchell, M.D.	4
A Contribution to Hemophilia, with Special Reference to the Joint Symptoms of the Disease. By Francis P. Kinnicutt, M.D.	15
Some Phases of the Neurotic Heart. By Beverley Robinson, M.D.	29
Chronic Poisoning by Acetanilid. By D. D. Stewart, M.D.	47
Intrapleural Lipoma; Acute Pericarditis; Pericardial Exploration. By R. H. Fitz, M.D.	57
Fever in Chronic Endocarditis. By John S. Thacher, M.D.	70
Rhythmic Lateral Displacement of the Heart as a Sign of Unilateral Pleuritic Exudate. By Charles Lyman Greene, M.D.	89
Acromegaly Associated with Symptoms of Myxedema. By Charles Lyman Greene, M.D.	93
Epigastric Linea Alba Hernia as a Little Recognized Source of Abdominal Pain and of Gastric Symptoms. By D. D. Stewart, M.D.	96
Concerning the Obscurity of Diagnosis Sometimes Attending Stone in the Kidney; with Report of Cases. By D. D. Stewart, M.D.	108
Chylous and Chyliform Effusions into the Serous Sacs; with a Case. By J. C. Wilson, M.D.	142
Sphygmograms from Two Cases of Bradycardia. By George Dock, M.D.	158

PAGE

Further Observations on the Relation of Lesions of the Gasserian and Posterior Root Ganglia to Herpes, Occurring in Pneumonia and Cerebrospinal Meningitis. By WILLIAM T. HOWARD, JR., M.D. 165

The Frequency and Etiology of Acute Non-tuberculous Pneumonia in a General Hospital. By WILLIAM TRAVIS HOWARD, JR., M.D. . 173

Some Considerations on Proteid Diet: with Especial Reference to Its Contents in Amide-nitrogen, Melanoidin-nitrogen, Diamino-nitrogen and Monamino-nitrogen. By LEWELLYS F. BARKER, M.D., and B. A. COHOE, M.D. 181

The Use of Nux Vomica in Hyperchlorhydria. By J. H. MUSSER, M.D. 193

Studies on the Toxicity of Bile. II. The Toxic Effects of Bile upon the Central Nervous System, Including a Study of the Elimination of Strychnin through Bile in Nephrectomized Animals. By S. J. MELTZER, M.D., and WILLIAM SALANT, M.D. 196

Xanthelasma and Chronic Jaundice. By THOMAS B. FUTCHER, M.B. (TOR.) 239

A Case of Lymphatic Leukemia in a Child. By JOHN LOVETT MORSE, A.M., M.D., and HARRY C. LOW, M.D. 254

Case of Lymphatic Leukemia. By F. FORCHHEIMER, M.D. . . 262

A Brief Report on Research in the Writer's Laboratory on Bacterial Toxins and Immunity. By VICTOR C. VAUGHAN, M.D. . . 265

A Case of Acute Leukemia, with Some Striking Clinical Features. Observations on Metabolism in this Case, and in a Case of Severe Purpura Hemorrhagica. By DAVID L. EDSALL, M.D. . . . 278

A Study of Metabolism in Leukemia, under the Influence of the x-Ray, with a Consideration of the Manner of Action of the x-Ray and of Some Precautions Desirable in its Therapeutic Use. By JOHN H. MUSSER, M.D., and DAVID L. EDSALL, M.D. . . 293

Remarks on Treatment of Cardiospasm by New Esophageal Dilator. By BERTRAM W. SIPPY, M.D. 324

Intestinal Perforation in Typhoid Fever in Early Life. By J. P. CROZER GRIFFITH, M.D. 328

Hematemesis from Gastric Ulcer; Notes on Over Two Hundred Cases. By W. GILMAN THOMPSON, M.D. 339

The Pathologic Anatomy of Exophthalmic Goitre. Preliminary Report. By W. G. MACCALLUM, M.D. 352

The Nature and the Lesions of Cirrhosis of the Liver, with Special Reference to the Regeneration and Rearrangement of the Liver Parenchyma. By A. O. J. KELLY, M.D. 356

Report of a Case of Pneumococcus Sepsis. By JOHN S. THACHER, M.D. 379

A Contribution to the Study of the Etiology of Tropical Ulcer. By RICHARD P. STRONG, M.D. 383

Chronic Acetanilid Poisoning, with Report of a Case Due to Absorption of the Drug from an Ulcer of the Leg. (Abstract.) By JAMES B. HERRICK, M.D., and E. E. IRONS, M.D. . . . 388

PAGE
On Gonorrheal Septicemia and Endocarditis. By W. S. Thayer, M.D. 391
The Chlorid Exchanges in Nephritis, with Special Reference to the Dechloridation Treatment. By A. O. J. Kelly, M.D., and Charles A. Fife, M.D. 428
The Elimination of Chlorids in Nephritis. By Joseph L. Miller, M.D. 431
The Relation of Stomach Disorders to Diabetes Mellitus. By John P. Sawyer, M.D. 446
Calcareous Degeneration. By Oskar Klotz 470
Experimental Arteriosclerosis. By Richard M. Pearce, M.D., and E. MacD. Stanton, M.D. 513
Peripheral Phlebosclerosis. By C. F. Martin, B.A., M.D., and J. C. Meakins, M.D. 525
On the Use of Opium in Myocarditis, Weak Heart and Dilated Heart. By J. H. Musser, M.D. 534
The Constituent of the Bile Causing Pancreatitis. By Simon Flexner, M.D. 537

ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1905-1906.

PRESIDENT.

FRANK BILLINGS, M.D.

VICE-PRESIDENT.

FRANCIS P. KINNICUTT, M.D.

SECRETARY.

HENRY HUN, M.D.

RECORDER.

SOLOMON SOLIS COHEN, M.D.

TREASURER.

J. P. CROZER GRIFFITH, M.D.

COUNCILLORS.

CHARLES G. STOCKTON, M.D.
V. C. VAUGHAN, M.D.
GEORGE M. KOBER, M.D.
F. FORCHHEIMER, M.D.
T. MITCHELL PRUDDEN, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.

WILLIAM OSLER, M.D.

ALTERNATE REPRESENTATIVE.

FRANCIS H. WILLIAMS, M.D.

OFFICERS OF THE ASSOCIATION

FROM ITS ORGANIZATION TO THE PRESENT TIME.

Year.	*President.*	*Vice-President.*	*Recorder.*	*Secretary.*	*Treasurer.*
1886.	Francis Delafield.	.....	.....	James Tyson.	A. B. Ball.
1887.	S. Weir Mitchell.	Francis Minot. R. Palmer Howard.	J. T. Whittaker.	Geo. L. Peabody.	W. W. Johnston.
1888.	Wm. H. Draper.	Francis Minot. R. Palmer Howard.	William Osler.	Henry Hun.	W. W. Johnston.
1889.	Francis Minot.	R. Palmer Howard. S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.

MEMBERS.

* Original Members.

ELECTED

1892. Abbott, Alexander C., Laboratory of Hygiene, University of Pennsylvania, Philadelphia.
1896. Abel, John J., Station L, St. Charles Ave., Baltimore.
1894. Adami, J. George, Pathological Laboratory, McGill University, Montreal, Canada.
1905. Adams, Samuel S., 1 Dupont Circle, Washington.
1896. Adler, Isaac, 12 East 60th St., New York.
1905. Babcock, Robert H., 100 State St., Chicago.
1899. Barker, L. F., Johns Hopkins University, Baltimore.
*1886. Baumgarten, G., 4900 Berlin Ave., St. Louis.
1894. Biggs, Herman M., 5 West 58th St., New York.
1895. Billings, Frank, 100 State St., Chicago.
1898. Blackader, A. D., 236 Mountain St., Montreal, Canada.
1901. Blumer, George, 369 Sutter St., San Francisco, Cal.
1892. Bolton, B. Meade, 4201 Maryland Ave., St. Louis.
1890. Bond, Charles S., 112 North 10th St., Richmond, Ind.
1898. Brannan, John W., 11 West 12th St., New York.
1888. Bridge, Norman, 217 S. Broadway, Los Angeles, Cal.
1904. Brown, Philip King, 1303 Van Ness Ave., San Francisco, Cal.
1899. Cabot, R. C., 190 Marlborough St., Boston.
1889. Cary, Charles, 340 Delaware Ave., Buffalo, N. Y.
1898. Cohen, Solomon Solis, 1525 Walnut St., Philadelphia.
1904. Collins, Joseph, 32 West 38th St., New York.
*1886. Councilman, Wm. T., 78 Bay State Road, Boston.
1894. Cutler, Elbridge G., 214 Beacon St., Boston.
1888. Dana, Charles L., 50 West 46th St., New York.
1888. Danforth, I. N., 905 West Monroe St., Chicago.
*1886. Delafield, Francis, 12 West 32d St., New York.
1893. Dock, George, 1014 Cornwell Place, Ann Arbor, Mich.
1904. Edsall, D. L., 1432 Pine St., Philadelphia.
1901. Edwards, Arthur R., 100 State St., Chicago.

ELECTED

1899. Ely, John S., 60 Wall St., New Haven, Conn.
1888. Ernst, Harold C., 8 Greenough Ave., Jamaica Plain, Mass.
1900. Ewing, James, 260 West 57th St., New York.
1904. Finley, Frederick G., 1013 Dorchester St., Montreal, Canada.
1895. Fischel, W. E., 2647 Washington Ave., St. Louis.
*1886. Fitz, Reginald H., 18 Arlington St., Boston.
1895. Flexner, Simon, Rockefeller Institute for Medical Research, corner Lexington Ave. and 15th St., New York.
*1886. Forchheimer, F., 160 West 9th St., Cincinnati, Ohio.
1894. Fussell, M. Howard, 189 Green Lane, Manayunk, Philadelphia.
1903. Futcher, Thomas B., 3 West Franklin St., Baltimore.
1904. Gordinier, H. C., 89 4th St., Troy, N. Y.
1901. Greene, Charles L., 150 Lowry Arcade, St. Paul.
1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1890. Hare, Hobart A., 1801 Spruce St., Philadelphia.
1897. Hektoen, Ludwig, Rush Medical College, Chicago.
*1886. Henry, Frederick P., 1635 Locust St., Philadelphia.
1898. Herrick, James B., 200 Ashland Boulevard, Chicago.
1898. Herter, C. A., 819 Madison Ave., New York.
1900. Holt, L. E., 14 West 55th St., New York.
1901. Howard, Wm. T., Jr., 88 Dorchester Ave., Cleveland, Ohio.
*1886. Hun, Henry, 149 Washington Ave., Albany, N. Y.
1901. Jackson, Henry, 380 Marlborough St., Boston.
*1886. Jacobi, A., 19 East 47th St., New York.
1899. James, Walter B., 17 West 54th St., New York.
*1886. Janeway, E. G., 36 West 40th St., New York.
1902. Joslin, E. P., 517 Beacon St., Boston.
1902. Kelly, A. O. J., 1911 Pine St., Philadelphia.
*1886. Kinnicutt, Francis P., 39 East 35th St., New York.
1901. Kinyoun, J. J., Glenolden, Pa.
1902. Kober, Geo. M., 1600 T St., N. W., Washington, D. C.
1900. Koplik, Henry, 692 Madison Ave., New York.
1895. Lafleur, Henri A., 58 University St., Montreal, Canada.
1888. Lewis, Morris J., 1316 Locust St., Philadelphia.
*1886. Longstreth, Morris, 1416 Spruce St., Philadelphia.
1905. MacCallum, A. B., University of Toronto, Toronto, Canada.
1902. MacCallum, W. G., Johns Hopkins Hospital, Baltimore.
1898. Mallory, F. B., Department of Pathology, Harvard Medical School, Boston.

ELECTED

1903. Martin, Charles F., 33 Durocher St., Montreal, Canada.
1905. McCrae, Thomas, 935 St. Paul St., Baltimore.
1891. McPhedran, A., 151 Bloor St., Toronto, Canada.
1892. Meltzer, S. J., 107 West 122d St., New York.
1905. Meyer, Adolf, Pathological Institute, Ward's Island, New York.
1905. Miller, Joseph L., 100 State St., Chicago.
1898. Mitchell, John K., 1730 Spruce St., Philadelphia.
*1886. Mitchell, S. Weir, 1730 Spruce St., Philadelphia.
1901. Morse, John Lovett, 70 Bay State Road, Boston.
1887. Musser, John H., 1927 Chestnut St., Philadelphia.
1891. Northrup, W. P., 57 East 79th, St., New York.
1900. Novy, F. G., University of Michigan, Ann Arbor, Michigan.
1902. Opie, E. L., Rockefeller Institute for Medical Research, corner Lexington Ave. and 15th St., New York.
*1886. Osler, Wm., 1 West Franklin St., Baltimore.
1899. Park, Wm. H., 315 West 76th St., New York.
*1886. Peabody, Geo. L., 57 West 38th St., New York.
1904. Pearce, R. M., 222 State St., Albany, N. Y.
1898. Pfaff, Franz, 29 Gloucester St., Boston.
1903. Preble, Robert B., 103 State St., Chicago.
1899. Prince, Morton, 458 Beacon St., Boston.
*1886. Prudden, T. Mitchell, 160 West 59th St., New York.
*1886. Putnam, James J., 106 Marlborough St., Boston.
1894. Rachford, B. K., 117 Broadway, Cincinnati.
1904. Richardson, Mark W., 2 Acorn St., Boston.
1905. Riesman, David, 1624 Spruce St., Philadelphia.
1893. Rotch, T. M., 197 Commonwealth Ave., Boston.
1898. Sachs, B., 21 East 65th St., New York.
1900. Sears, George G., 19 Marlborough St., Boston.
1900. Sewall, Henry, Majestic Building, cor. Broadway and Sixteenth St., Denver, Col.
*1886. Shattuck, Frederick C., 135 Marlborough St., Boston.
*1886. Sinkler, Wharton, 1606 Walnut St., Philadelphia.
1902. Sippy, B. W., 103 State St., Chicago.
*1886. Smith, A. A., 18 West 51st St., New York.
1892. Smith, Theobald, South St., Forest Hills, Boston.
1887. Starr, M. Allen, 5 West 54th St., New York.
1898. Stengel, Alfred, 1811 Spruce St., Philadelphia.

ELECTED

*1886. Sternberg, George M., 2144 California Ave., N. W., Washington, D. C.
†1896. Stewart, D. D., 1633 Spruce St., Philadelphia.
*1886. Stewart, James, 285 Mountain St., Montreal, Canada.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
1904. Strong, Richard P., Bureau of Government Laboratories, Manila, P. I.
1899. Thacher, J. S., 839 Madison Ave., New York.
1897. Thayer, W. S., 406 Cathedral St., Baltimore.
1889. Thompson, W. Gilman, 34 East 31st St., New York.
1889. Thomson, Wm. H., 23 East 47th St., New York.
*1886. Trudeau, Edward L., Saranac Lake, Franklin Co., N. Y.
*1886. Tyson, James, 1506 Spruce St., Philadelphia.
1889. Vaughan, Victor C., University of Michigan, Ann Arbor, Mich.
1898. Vickery, Herman F., 263 Beacon St., Boston.
*1886. Ward, Samuel B., 281 State St., Albany, N. Y.
1901. Warthin, Aldred S., University of Michigan, Ann Arbor, Mich.
*1886. Welch, Wm. H., 935 St. Paul St., Baltimore.
1898. Wesbrook, F. F., State Board of Health, Minneapolis, Minn.
*1886. Wilkins, George, 899 Dorchester St., Montreal, Canada.
1894. Williams, Francis H., 505 Beacon St., Boston.
1901. Williams, Herbert U., University of Buffalo, Buffalo, N. Y.
*1886. Wilson, James C., 1509 Walnut St., Philadelphia.
1898. Withington, Charles F., 35 Bay State Road, Boston.
*1886. Wood, Horatio C., 1925 Chestnut St., Philadelphia.
1899. Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

† Died June 13, 1905.

ASSOCIATE MEMBERS.

ELECTED

1905. Capps, Joseph A., 100 State St., Chicago.
1905. Christian, Henry, 688 Boylston St., Boston.
1905. Conner, Lewis A., 53 East 49th St., New York.
1905. Janeway, Theodore, 36 West 40th St., New York.
1905. Sailer, Joseph, 248 S. 21st St., Philadelphia.
1905. Steele, J. Dutton, cor. 40th and Locust Sts., Philadelphia.
1905. Taylor, A. E., 2515 Octavia St., San Francisco.

HONORARY MEMBERS.

Elected Active Member	Elected Honorary Member	
1886.	1905.	Atkinson, I. E., 609 Cathedral St., Baltimore.
1886.	1902.	Ball, A. Brayton, 42 West 36th St., New York.
1886.	1887.	Billings, John S., Astor Library, Lafayette Place New York.
1886.	1897.	Chew, Samuel C., 215 West Lanvale St., Baltimore.
1897.	1905.	Cushny, Arthur C., University of London, London, Eng.
1886.	1905.	Edes, Robert T., 340 Summer Ave., Reading, Mass.
1890.	1902.	Fisk, S. A., Denver Club, Denver, Col.
1886.	1901.	Folsom, Charles F., 15 Marlborough St., Boston.
1886.	1900.	Guitéras, John, Havana, Cuba.
1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1890.	1905.	Latimer, Thomas S., 211 West Monument St., Baltimore.
1889.	1904.	Loving, Starling, 229 East State St., Columbus, Ohio.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1887.	1905.	Meigs, Arthur V., 1322 Walnut St., Philadelphia.
1886.	1897.	Miles, F. T., 514 Cathedral St., Baltimore.
1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
1886.	1904.	Robinson, Beverley, 37 West 35th St., New York.
1886.	1905.	Shattuck, George B., 183 Beacon St., Boston.
1891.	1905.	Smith, Andrew H., 18 East 46th St., New York.
1887.	1902.	Starr, Louis, 1818 S. Rittenhouse Square, Philadelphia.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.

DECEASED MEMBERS.

* Honorary Members.

Date of Election	
*1890.	Barker, Fordyce, New York.
*1886.	Bowditch, Henry I., Boston.
1886.	Bruen, Edward T., Philadelphia.
1886.	Busey, Samuel C., Washington, D. C.
*1886.	Clark, Alonzo, New York.
*1886.	Clymer, Meredith, New York.
1886.	Da Costa, J. M., Philadelphia.
1889.	Dabney, William C., University of Virginia.
*1886.	Dalton, John C., New York.
*1886.	Dana, Israel T., Portland, Maine.
1886.	Donaldson, Frank, Baltimore.
1886.	Draper, William H., New York.
1886.	Formad, Henry F., Philadelphia.
1889.	Geddings, W. H., Aiken, S. C.
1886.	Graham, J. E., Toronto, Canada.
1886.	Howard, R. Palmer, Montreal, Canada.
1886.	Hudson, E. Darwin, Jr., New York.
1886.	Hutchinson, James H., Philadelphia.
1886.	Johnson, Hosmer A., Chicago.
1899.	Johnston, W. G., Montreal, Canada.
1886.	Johnston, W. W., Washington, D. C.
*1886.	Leidy, Joseph, Philadelphia.
1886.	Loomis, Alfred L., New York.
1886.	Lyman, Henry M., Chicago.
1890.	MacDonnell, R. P., Montreal, Canada.
1886.	McBride, Thomas A., New York.
*1886.	Metcalf, John T., Cold Spring, N. Y.
1886.	Minot, Francis, Boston.
1898.	Packard, Frederick A., Philadelphia.
1886.	Pepper, William, Philadelphia.
1888.	Prentiss, D. W., Washington, D. C.

Date of Election

1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo. N. Y.
1889. Roosevelt, J. West, New York.
1886. Ross, George, Montreal, Canada.
1886. Schmidt, H. D., New Orleans.
*1886. Stillé, Alfred, Philadelphia.
1886. Thacher, James K., New Haven, Conn.
1886. Whittaker, James T., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION.

As Amended May 16, 1905.

Article I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II.

Members.

The number of active members shall be limited to one hundred and thirty-five. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to honorary membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting in the City of Washington, D. C., at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology and miscellaneous business.

4. Authors of papers and referees and co-referees who open a discussion shall not occupy more than thirty minutes each; and in the discussion following, the remarks of each speaker shall be limited to ten minutes.

5. The referee, co-referee and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution, twenty-five members shall be necessary.

Article VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee, and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall

take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X.

Amendments to the Constitution,

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

TWENTIETH ANNUAL MEETING.

Held at Washington, D. C., May 16 *and* 17, 1905

The following members were present during the meeting:

A. C. Abbott,
J. J. Abel,
J. G. Adami,
L. F. Barker,
G. Baumgarten,
H. M. Biggs,
F. Billings,
B. M. Bolton,
R. C. Cabot,
C. Cary,
S. S. Cohen,
J. Collins,
I. N. Danforth,
D. L. Edsall,
J. Ewing,
F. G. Finley,
R. H. Fitz,
F. Forchheimer,
M. H. Fussell,
T. B. Futcher,
H. C. Gordinier,
C. L. Greene,
J. P. C. Griffith,
H. A. Hare,
H. Hun,
H. Jackson,
A. Jacobi,
W. B. James,
E. G. Janeway,
E. P. Joslin,
A. O. J. Kelly,
F. P. Kinnicutt,
J. J. Kinyoun,
G. M. Kober,
H. A. Lafleur,
M. Longstreth,
W. G. MacCallum,
A. McPhedran,
C. F. Martin,
S. J. Meltzer,
J. K. Mitchell,
S. W. Mitchell,
J. L. Morse,
J. H. Musser,
W. P. Northrup,
W. Osler,
G. L. Peabody,
R. M. Pearce,
R. B. Preble,
T. M. Prudden,
M. W. Richardson,
T. M. Rotch,
B. W. Sippy,
A. Stengel,
G. M. Sternberg,
D. D. Stewart,
J. S. Thacher,
W. S. Thayer,
W. G. Thompson,
E. L. Trudeau,
J. Tyson,
V. C. Vaughan,
W. H. Welch,
G. Wilkins,
F. H. Williams,
H. U. Williams,
J. C. Wilson,
J. H. Wright.

Tuesday, May 16th.—Morning Session.

The Association was called to order at 10 A.M. by President Trudeau, who read the President's Address.

The Treasurer read his report, which was referred to an Auditing Committee consisting of Drs. Cohen and W. G. Thompson.

It was resolved that Article II. of the Constitution be amended by inserting, after the first paragraph of the article, a paragraph stating "There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member."

It was resolved that Article II. of the Constitution be amended by the insertion of the following paragraph: An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to honorary membership.

The suggested amendment to the Constitution requiring honorary members to pay annual dues of five dollars was not adopted.

The Secretary announced that the Council had fixed the annual dues for the ensuing year at $12.00.

The Secretary then read the names of those nominees recommended by the Council for election.

Dr. S. Weir Mitchell read a paper entitled "A Study of the Fear of Cats and of the Power to Recognize their Presence when Unseen and Unheard," which was not discussed.

Dr. Fitz read a paper entitled "Intrapleural Lipoma and Pericardial Exploration," which was discussed by Drs. Ewing, Osler, F. H. Williams, Northrup, Forchheimer and Peabody.

Dr. Greene read a paper entitled "Rhythmic Lateral Displacement of the Heart as a Sign of Unilateral Pleuritic Exudate," which was not discussed.

Dr. Thayer read a paper entitled "Gonorrheal Septicemia and Endocarditis," which was discussed by Dr. Osler.

Dr. Thacher read a paper entitled "Fever in Chronic Endocarditis," which was discussed by Drs. W. G. Thompson, Kelly, J. K. Mitchell, Jacobi, Tyson, Preble, Vaughan, Osler, Kinnicutt and Thacher.

Dr. Kinnicutt read a paper entitled "Some Cases of Hemophilia, with Special Reference to the Joint Symptoms of the Disease," which was not discussed.

Dr. Musser read a paper entitled "Clinical Notes on Opium in Myocarditis," which was discussed by Drs. Fussell, Robinson, Jacobi and McPhedran.

Dr. Robinson read a paper entitled "Some Phases of the Neurotic Heart," which was not discussed.

The Auditing Committee reported that they had examined the Treasurer's report and vouchers and found them to be correct.

Adjourned at 1.15 P.M.

Afternoon Session.

The Association was called to order at 2.35 P.M. by Vice-President Billings.

Dr. Thacher read a paper entitled "Report of a Case of Pneumococcus Sepsis," which was not discussed.

Dr. Griffith read a paper entitled "A Report of Six Cases of Perforation in Typhoid Fever in Children," which was discussed by Drs. Jacobi and Peabody.

Dr. W. G. Thompson read a paper entitled "Hematemesis from Gastric Ulcer, Notes on 200 Cases," which was discussed by Drs. Kinnicutt, Cohen, Sippy, Musser and Thompson.

Dr. John S. Sawyer, of Cleveland, read a paper entitled "The Relation of Certain Stomach Disorders to Diabetes Mellitus," which was discussed by Drs. Tyson, Kelly, Cohen and Sawyer.

Dr. Musser read a paper entitled "Clinical Notes on the Use of Nux Vomica, Especially in Certain Forms of Hyperchlorhydria," which was discussed by Drs. Tyson, Stewart and Musser.

Dr. Stewart read a paper entitled "Supraumbilical Hernia as a Little-recognized Source of Abdominal Pain," which was not discussed.

Dr. Stewart read a paper entitled "Stone in the Kidney and Certain Conditions Simulating It," which was discussed by Drs. Danforth, Tyson, Forchheimer and Billings.

Dr. Cabot read a paper entitled "A Study of Abdominal Tumors," which was discussed by Drs. Fussell, Thayer, Kinnicutt, Jacobi, Musser, Cohen and Danforth.

Dr. Sippy gave a demonstration of a method of treating spasm of the cardiac orifice of the stomach.

Adjourned at 5 P.M.

WEDNESDAY, MAY 17TH.—MORNING SESSION.

The Association was called to order at 10.10 A.M. by President Trudeau. The nominations for officers made by the Council were read.

The following members and associate members were elected to the Association:

ACTIVE MEMBERS.—A. B. MacCallum, of Toronto; David Riesman, of Philadelphia; Adolf Meyer, of New York; J. L. Miller, of Chicago, R. H. Babcock, of Chicago; Thos. McCrae, of Baltimore; S. S. Adams, of Washington.

ASSOCIATE MEMBERS.—J. D. Steele, of Philadelphia; Joseph Sailer, of Philadelphia; Joseph A. Capps, of Chicago; Henry Christian, of Boston; A. E. Taylor, of San Francisco; L. A. Conner, of New York; Theodore Janeway, of New York.

Dr. Barker read a paper entitled "Considerations on Proteid Diet, with Especial Reference to the Distribution of Amido-nitrogen, Diamino-nitrogen and Monamino-nitrogen Therein," which was discussed by Dr. Vaughan.

Dr. Kelly read a paper entitled "The Chlorid Exchanges in Three Cases of Chronic Nephritis, with Reference to the Dechloridation Treatment," which was followed by a paper by Dr. Miller (read by Dr. Billings) entitled "Chlorid Retention in Nephritis." Both papers were discussed by Drs. Stengel, Kinnicutt, Edsall, Meltzer, Kober, Cabot, Sternberg, Jacobi, Collins, Tyson and Kelly.

Dr. Meltzer read a paper entitled "On the Toxicity of Bile," and one entitled "On the Nature and Origin of Cholemia and Uremia," which were discussed by Drs. Ewing, Cohen, Carroll and Meltzer.

Dr. Futcher read a paper entitled "Xanthelasma and Chronic Icterus," which was discussed by Drs. Jacobi and Futcher.

Dr. Morse reported a "Case of Lymphatic Leukemia in a child of three and one-half years," which was discussed by Drs. Forchheimer, Barker, Thayer, Welch and Morse.

The following officers were elected:

President—Frank Billings.
Vice-President—F. Kinnicutt.
Secretary—Henry Hun.
Recorder—Solomon Solis Cohen.
Treasurer—J. P. Crozer Griffith.
Councillor—T. Mitchell Prudden.

Adjourned at 1.10 P.M.

Afternoon Session.

The Association was called to order at 2.20 by Vice-President Billings.

Dr. Adami gave a lantern-slide demonstration "On the Stages of Calcareous Degeneration."

Dr. Pearce read a paper entitled "Experimental Arteriosclerosis, with Demonstration of Specimens."

Dr. Martin read a paper entitled "Phlebosclerosis." All three papers were discussed by Drs. Welch, Meltzer and Pearce.

Dr. Edsall read a paper entitled "Observations on Metabolism in a Case of Acute Leukemia and a Case of Purpura Hemorrhagica," and one entitled "The Influence of the *x*-Ray on Metabolism in Leukemia," which were discussed by Drs. Williams, Ewing, Barker and Edsall.

Dr. D. D. Stewart read a paper entitled "Chronic Acetanilid Poisoning," which was not discussed.

Dr. Vaughan read a paper entitled "A Brief Report on Recent Researches in the Writer's Laboratory on Bacterial Toxins and Immunity," which was discussed by Drs. Welch, Meltzer and Vaughan.

Dr. Greene read a paper entitled "Report of a Case of Acromegaly," which was discussed by Dr. Cohen.

Dr. Kelly read a paper entitled "The Nature of Cirrhosis of the Liver," which was discussed by Dr. Pearce.

Dr. MacCallum read a paper entitled "The Pathology of Exophthalmic Goiter," which was discussed by Drs. Kelly and MacCallum.

During the meeting the following papers were read by title.

"Report of a case of Chronic Acetanilid Poisoning through Absorption from an Ulcer," by James B. Herrick and E. E. Irons.

"Chylous and Chyliform Effusions into the Serous Sacs, with a Case," by J. C. Wilson.

"Sphygmograms from Two Cases of Bradycardia," by George Dock.

"The Frequency and Etiology of Acute Non-tuberculous Pneumonia in a General Hospital," by Wm. T. Howard, Jr.

"Further Observations on the Relation of Lesions of the Gasserian and Posterior Root Ganglia to Herpes Occurring in Pneumonia and Cerebrospinal Meningitis," by Wm. T. Howard, Jr.

"A Note with a Demonstration upon Experimental Pancreatitis," by Simon Flexner.

"A Contribution to the Etiology of Tropical Ulcer," by Richard P. Strong.

The thanks of the Association were tendered to the Hotel Willard for the courtesy of a room for the meeting. By a rising vote the thanks of the Association were tendered to Dr. Trudeau for his courtesy and self-sacrifice in presiding over the meeting.

Adjourned at 4.30 P.M.

HENRY HUN,
Secretary

ADDRESS OF THE PRESIDENT.

By E. L. TRUDEAU, M.D.,
OF SARANAC LAKE, N. Y.

Gentlemen: I wish I could fully express my appreciation of the great honor conferred upon me in my election as President of this Association.

I do not know which I have prized the most, the invitation I received nineteen years ago to become one of the original members, my election last year as President, or the pleasure and satisfaction of meeting the members at the sessions of the Association and joining in its work since 1886.

Those of us who can look back to that time must feel that our Association has certainly lived up to its ideals, and has more than fulfilled its destiny along the lines laid down by its founders. Its sessions have ever been free from medical politics and from personal and ethical disputes, and the time and talents of its members have been solely devoted to the presentation of original observations and researches, and to the discussions and consideration of scientific medicine in its broadest sense.

It has led the way—and has been instrumental in bringing about the more scientific and exact methods which obtain in medicine to-day—in encouraging research work in every field of medicine, and its Transactions teem with valuable original observations and papers which report some of the most noted advances in the history of American medicine. It has remained an arena where the clinician and the laboratory worker, the general practitioner and the scientist, might meet on common ground, and where the claims of all methods tending to the advancement of medical science could be impartially scrutinized.

While retaining its own broad basis as an association of American physicians, it has stimulated the growth of many new societies devoted to special lines of work. If it is to continue to have brought before it at its meetings the best observations and most promising researches of the day, and to pass upon their practical value to internal medicine, if it is to keep up its traditions and the extent and character of its work in the future, it must adapt itself to the growth and changes taking place in every field of medicine and draw in new life and energy by a constant accession of young men who are at the height of their activities in both clinical and laboratory work.

The increase of active membership, the proposed amendments to the constitution relating to associate members and voluntary retirement of active members are steps in the right direction.

We have lost by death during the past year one of our fellow-members, Dr. Henry M. Lyman, who died at Evanston, Illinois, November 21, 1904. Dr. Lyman was one of the original members of this Association. He was born at Hilo, Hawaii, in 1835, and was graduated from Williams College, Massachusetts, in 1853, and in 1861 from the College of Physicians and Surgeons in the city of New York. In both colleges he was the valedictorian of his class. From 1871 to 1900 he held, successively, the positions of Professor of Chemistry, Professor of the Diseases of the Nervous System, Professor of Physiology and Professor of Theory and Practice in Rush Medical College, and subsequently became Dean of the Faculty. He was attending physician to Cook County Hospital, Chicago, and to the Presbyterian Hospital from 1884 until his retirement. He held also many other positions of trust in medical societies and as professor and editor. His chief contributions to literature are his works on *Artificial Anesthesia and Anesthetics, Insomnia* and the other disorders of sleep, and a text-book on the *Theory and Practice of Medicine,* besides numerous articles in medical literature.

No words of eulogy are necessary. Dr. Lyman has left a record of which this Association may well be proud, and he will be sadly missed by the community, the profession and his fellow-members.

The departure from this country of two of our members, Dr. Arthur C. Cushny and Dr. William Osler, who have been called

to fill positions of honor and trust abroad, will prove a serious loss to us all. Dr. Cushny, who has occupied the position of Professor of Materia Medica and Therapeutics at the University of Michigan (Ann Arbor), has been called to a professorship in the University of Medicine in London. He became a member of our Association in 1897, and will be greatly missed from our midst.

Dr. William Osler, as you all know, has accepted the Regius Professorship of Medicine at Oxford and will hereafter live in England. I feel my inability to suitably express the incalculable loss which Dr. Osler's departure from among us must prove, not only to this Association, but to the entire profession of this country. His brilliant attainments and indefatigable energy, his valuable contributions and the great interest he always took in this Association, in the formation of which he was one of the prime movers, have contributed in no small measure to make it what it is to-day. His genial disposition and his striking personality have bound so many of us to him by such strong ties of friendship that after he has left us his heart will by no means be the only one to show "cardiac cicatrices." His great name, his teachings and his example are left to us as a precious heritage and ever-present inspiration. Our best wishes and much more that I cannot say here go with him to the new field of his labors.

OF AILUROPHOBIA AND THE POWER TO BE CONSCIOUS OF THE CAT AS NEAR, WHEN UNSEEN AND UNHEARD.

By S. WEIR MITCHELL, M.D.,
OF PHILADELPHIA.

Three years ago I was consulted in regard to the case of an hysteric young woman in whom the fear of cats had become an obsession. She declared that she could always detect the presence of an unseen and unheard cat. Since, however, she was constantly announcing the presence of a cat, it was not surprising that, like a clock that has stopped and tells the time correctly twice in the twenty-four hours, her occasional successes confirmed her belief. Her failures had of course no contradictory value.

I saw her three times and on each occasion she said there was a cat in the room. It was true at her first visit, although she could not have seen it. It was untrue of two later visits; but each time she exhibited the same fear and the usual mild hysteric manifestations.

A second case was, I felt sure, an exhibition of real capacity to know when the unseen and unheard cat was present. It came to my knowledge later.

The two cases led me to inquire further into the matter. Except concerning asthma, variously due to the presence of cats, dogs, rabbits, horses or sheep, I found no available medical literature. When the power to know an unseen cat as nearby was mentioned, it was usually with entire skepticism, nor where it was believed to be true was any explanation attempted.

In order to collect material for study, I asked through a medical journal (*American Medicine*) answers to the following questions:

A. 1. Have you any antipathy to cats?
2. Are you subject to unusual feelings or symptoms in the presence of a cat?
3. What are these?
4. Does the presence of a tiger in a menagerie affect you as do cats?
5. Can you account for your cat fear by anything obvious, as, for example, any incident of childhood?
6. At what age did you first discover your peculiarity as to cats?

B. 1. Are you surely aware of the presence of a cat when it is not in sight, or known to be near?
2. If yes, give the evidence, your own, and that of others as to the fact.
3. What feelings or symptoms make you sure of the cat's presence?
4. Is it the cat odor?
5. How long have you had this peculiarity?

The request was widely copied, and I received 159 replies from persons in America, England and Germany. Many were from well-known persons—professors, army officers, physicians and the like. About a third were valueless. A few were from men or women who were personally well known to me, and who I am certain may be trusted. The general result was to give me a body of evidence of great interest and to furnish me with some indicative hints as to the cause, not so much of cat fear as of the more curious question concerning the ability of certain people to be sure of the neighborhood of unseen cats.

Many of the cases I do not use. They are simply examples of cat asthma in confirmed asthmatic sufferers. This disorder is well known, and is sufficiently dealt with in the books on asthma, especially Bramwell.[1] One of my answers is from Mr. S., whose case is well reported by Dr. Salter.[2] These cases are not always associated with dread or even dislike of cats as such, and do not concern my present object any more than do the asthmas caused by roses, oranges or apples.

My research brought me indisputable evidence concerning the large number of people in whom the irritating presence of a cat gives rise to a variety of symptoms. In such persons the feeling caused by seeing a cat is instantaneous. In the asthma victims it is slower, cumulative and may not be felt at all for

[1] Camerari, Felisantipathia. Clinical Studies, Edinburgh, 1901–03, N. S., 1, p. 330.
[2] The Lancet, 1866, p. 384.

twenty minutes or more. Certain persons on seeing a cat have other symptoms, with or without oppression of breathing. There may be only fear, terror, disgust; there may be added chilly sensations, horripilation, weakness, locked jaw, or, as in one case, fixed, open jaw, rigidity of arms, pallor, nausea, rarely vomiting, pronounced hysteric convulsions and even temporary blindness. These pass away with removal of the cat, but in a few examples leave the sufferer nervously disturbed for a day. Two report themselves as apt to have dreams of cats, what one of them calls "cat-mares."

Five persons, three being women, are alarmed in the presence of the greater cats—caged tigers or lions. A soldier of great distinction, much given when younger to tiger hunting, is undisturbed by these great felines but terrified by the tame cat.

To Question 5, first series, "Can you account for the origin of your dread?" the general reply is negative. Three assign it to their having been scared by a cat in childhood and one to a prenatal incident affecting the mother. Nothing of value was obtained.

Question 6. Everyone answered that the simple fear dated from early childhood, but that the symptoms of weakness, nausea, chilliness and the more distinct hysteric signals, like rigidity, etc., came on later and increased after puberty. Three women and two men report the symptoms as lessening in middle age, and several have resolutely overcome that which had grown to be a serious inconvenience.

At least a fourth of my cases of cat terror in grave forms speak of it as a family peculiarity. Five members of one family of seven had it. In another case a maternal grandfather, two great aunts, an uncle and a sister were all thus troubled; and in other families where one had it, at least one other, a brother or sister, was more or less affected. Single cases in families were, however, the rule.

Sex appears to have no marked influence, but the extreme symptoms are more frequent in women.

Aversion to cats is well known to have disturbed many historic personages and is alluded to in a well-known passage of Shakespeare. The other matter with which this paper is concerned is of far more interest. It is dealt with in my second set of questions.

Question B, 1, asks: "Are you surely conscious of the presence of a cat when it is not in sight and not otherwise known to be near?" Very fortunately my best and most trustworthy evidence has been as to this part of the investigation.

After careful study of the replies, much sequent inquiry and rejection of all doubtful cases, I reached the conclusion that as concerns thirty-one persons I had evidence enough to make me sure that they could tell when a cat was near, although neither seen nor heard. Three of my most intelligent witnesses, two of them personally known to me, say that usually they possess this power and at other times they do not. One of them thinks that she more rarely detects well-cared-for cats, but always recognizes a stray invader from the street and gives instances in point.

On a study of the two sets of cases—those who at sight of cats have fear, horror and, in varying degrees, emotional disturbances and distinct physical symptoms and those whom unseen cats affect in like manner—we observe that the same symptomatic expressions attend both sets of cases.

In the first case sight of the cat informs; then there is fear, horror, disgust and more or less of the nervous symptoms already described. In the second set, those who are conscious of unseen cats, some sense other than sight or hearing gives the information, and then the symptoms are, as I have said, much the same as when the cat is seen.

The most interesting question concerns the means by which assurance is reached of the presence of the unseen animal. This examination must necessarily include all cases, the asthmatics and those in whom the resultant signals are not asthmatic, but merely what may be called nervous or even hysterical. Asthmatic patients who suffer from animal emanations are not usually aware of the odor as present if the cause be a cat. Several declare, and one is an acute observer, that woollens on which an animal has been lying may occasion asthma although the patient may perceive no smell.

Four of the thirty-one who recognize an unseen cat as near declare that they know it because of the odor of the animal. The remaining twenty-seven, some of them trained observers—physicians, engineers, a soldier of distinction and certain very intelligent and healthy-minded women—are positive that they do not

smell the cat and that they are absolutely ignorant of the mode in which they become aware of the presence of the offending animal. Accepting their evidence as beyond doubt true, how shall we account for the facts?

We must admit that all animals and human beings emit emanations which are recognizable by many animals and are in wild creatures protectively valuable.

This delicate recognition is commonly lost in mankind, but some abnormal beings, like Laura Bridgeman and a perfectly normal lad I once saw, have possessed the power of distinguishing by smell the handkerchiefs of a family after they had been washed and ironed. In this lad I made a personal test of his power to pick out by their odor from a heap of clean handkerchiefs mine and those of others, the latter two belonging to his father and mother.

I have seen a woman, well known to me, who can distinguish by mere odor the gloves worn by relatives or friends. This lady, who likes cats as pets, is able to detect by its odor the presence of a cat when I and others cannot.

Two French observers believe that they have proved the sense of olfaction to be nine times more acute in women than in men.[1]

So far as the present paper might serve in evidence, I should be inclined to say that the sense of smell was keener in women than in men, but as to this there is extreme diversity of opinion and the whole subject awaits further investigation.

Mr. Havelock Ellis, after considering all the testimony attainable at present, reaches the conclusion that the sense of smell is keener in men than in women. This may be the case in general, but I am perfectly certain that the highest degrees of sensitiveness as to smell are to be found in certain women and not necessarily in women who are of a hysteric nature or otherwise than healthy. How this question stands as to the male and female of sporting dogs may be worth inquiry.

Much has been said in a vague way about the effect of odors on man, but, although Beyer[2] has shown that in the rabbit certain odors increase and others retard the rate of respiratory movements, I am aware of no such experiments on man. It is,

[1] Toulouse et Vaschide. Soc. de Biologie, May, 1899.

[2] Arch. für Phys., 1901.

however, well known that no other of the senses is as capable of reviving memories, pleasant or unpleasant, as the sense of smell.

These remarks prepare us to consider the means by which certain persons are aware of the nearness of unseen cats and are thus thrown into a state of agitation and general nervousness. They are usually not conscious of the unseen cat as odorous.

It seems to me possible that either they smell the cat too slightly to be able to define the odor or else receive an olfactory impression of which they are not conscious as an odor, but only in the form of such symptoms as the visible cat would also evoke.

To be influenced by an olfactory impression of which (as odor) the subject rests unconscious may seem an hypothesis worthy of small respect and beyond power of proof. Nevertheless, it seems to me reasonable. There are sounds beyond the hearing of certain persons. If they ever cause effects, we do not know. There are rays of which we are not conscious as light or heat, except through the effects to which they give rise. There may be olfactory emanations distinguished by some as odors and by others felt, not as odors, but only in their influential results on nervous systems unusually and abnormally susceptible. No other explanation seems to me available, and this gains value from certain contributory facts.

One woman, a very trustworthy witness, writes to me that from childhood she has had fear of cats and, with great general acuteness of the sense of smell, had always been able when young to be sure an unseen cat was in the room because of the distinctive odor of the animal. When older and long married her olfactory sense became dull, so that, while sometimes certain that she could smell the unseen cat, at times she was uncertain. Occasionally she was very confident that a cat was near when there was no detectable odor and on these occasions was nearly always correct.

Either the odor in this case had nothing to do with recognition and we must seek an explanation elsewhere or the odor was just sufficient to set in motion the mechanism of habitually associated emotion and was not distinct enough or lasting enough to be felt as an odor.

No matter what the primary form of impression, association and memory have their share in the ultimate train of symptoms.

It is to be borne in mind that acute conjunctivitis is in a few victims caused by nearness of cats; that in rare examples the cat emanations cause cutaneous irritation; so that we may not be sure that it is only through emanations necessarily odorous that the train of symptoms is started and still it is sure that in many cases not only is there no perceptible odor, but no consciously felt nasal irritation.

An interesting illustration is unconnected with animals. A young man who had little keenness of the olfactory sense went abroad in bad health on a sailing ship. He was seasick, homesick, melancholy. When in the Mersey he first smelt English coal smoke. For years the odor brought a slight return of depression and sometimes before he recognized the cause. On one occasion, when walking in Wales, he said to a friend that he had been feeling the melancholy impressions coal smoke occasioned, but had not smelt any smoke. His friend said that he himself had smelt it for some minutes, but that it was barely perceptible. This seems to me to assist in explaining some of the cases of the detection of unseen cats. I could readily supply other cases of like nature.

To conclude, I am of opinion that emanations from cats, odorous to some, may in others cause emotional disturbance without so impressing the olfactory nerves as to be recognized as odors.

When we seek an explanation of the terror inspired by cats in a few persons, we are forced to fall back upon the inherited remainders of animal instincts of protective nature. This view is, however, weakened by the fact that in most of the worst cases of cat fear there is no terror in the presence of the lion.

This paper would be incomplete without a statement of some of the evidence I accept as proof that a limited number of those who have the fear of cats and suffer are conscious of their presence when they neither see nor hear them.

In my own family an uncle was the subject. My father, the late Professor John K. Mitchell, having placed a small cat in a closet, with a saucer of cream, asked Mr. H. to come into the room and look at some old books in which he would be interested. He sat down, but in a few minutes grew pale, shivered and said, "There is a cat in the room." Dr. M. said: "Look about you. There is no cat in the room. Do you hear one outside?" He said, "No, but there is a cat." He became faint and, complaining of nausea, went out and promptly recovered.

I quote the following from a physician of distinction as a case where the symptoms arise on seeing a cat, and where, at other times, they are evoked by the odor of an unseen cat.

My wife simply lives in horror of cats. It is more than fright, and it makes no difference whether it be a tiny kitten or the most tiger-like tomcat. I have seen her absolutely prostrated by terror after an unexpected meeting with a cat, although she is not in the least hysterically inclined nor afraid of other animals.

She has never as a child been frightened by a cat, but has always had this fear. She can usually detect a cat's presence by its smell when it is unseen and when others cannot smell it, but this she cannot always do. Her father has the cat fear and her maternal grandmother can also "smell out" a cat, also a brother and two sisters, the rest of a large family being indifferent to the animal.

A lady very well known to me sends me, with other instances, this: She was in her room preparing for bed when suddenly she felt her usual sensations of a cat being near. A servant was called and a vain search was made. At last, still suffering, she herself made a careful search and found a strange cat curled up under a lounge and well hidden. She has no knowledge of a cat from sense of smell.

Dr. J. C. W. writes me: "Some years ago I was present at a meeting of a scientific society. The secretary, while reading his report, stopped and said: 'I can't go on. There must be a cat in the room.' Search was made, and under the topmost seat in the amphitheatre was found a cat."

Mrs. C. Intense horror of cats, flush, chills, goose flesh, rigid jaws. It is an hereditation. When younger she could always know when a cat was near. This is in later years less certain. She no longer faints. She writes: "A striking instance of my sensitiveness occurred many years ago, but now my sensibility is far less acute and I was never able to smell a cat. I did not know how I knew of the animal as near. Becoming disturbed, as usual, while seated on a low veranda, I declared there must be a cat under my chair. A little later a cat crawled out from under the veranda. This was only one of several such experiences."

Mrs. H., a lady long and well known to me, first told me and later wrote to me to this effect: "I was in a shop in Paris trying on gloves when I became sure of a cat near me. The woman in charge said she had no cat, but on my persisting and becoming faint, search was made and a stray cat found under the counter and driven into the street. A few minutes later my symptoms returned and the cat was found to have come back into the shop through the open door and was behind me. I could recall a number of like instances."

Mrs. C., her mother, and her child, and a grandmother were all able to detect the presence of unseen cats, and the daughter declares that in her case it is unconnected with any odor.

Dr. S. reports a case to me of a lady who many times to her knowledge

became faint, pale and sick because of the presence of a cat, unseen at the time by her and by others, and is entirely confident that this is the case.

Dr. T. writes as follows: "General Roberdeau had an unaccountable aversion to being anywhere in the vicinity of cats. It was no affectation, but an inborn idiosyncrasy. He could not account for it and tried hard to overcome it, but without the least success. It affected him with a peculiar faintness, paleness and difficulty of breathing, increasing to such an extent that it was necessary for him to leave the room. He was never mistaken when he said there was a cat in the room, an instance of which occurred once when invited to dine at Chief Justice McKean's. Knowing his antipathy, they made careful search and aired the room, but the moment General Roberdeau entered he said, 'There is a cat here.' They assured him there was not, for they had taken proper precautions on his account. He replied that he knew there was a cat there and retired to another room, while a further search revealed a kitten behind the bookcase. The writer's father has often found his mother and aunts tell of their girlish tricks played on General Roberdeau, of secreting a cat in the room in which he was sitting and the general never failed to perceive it instantly.

"This peculiarity does not seem to be generally inherited among his descendants, except that in three or four cases it has appeared in a modified form. Mrs. Jane A. seemed in a limited degree to partake of her father's antipathy, as also her daughter, Mrs. M., who, although not affected to the same extent as her grandfather, has a great aversion to them without being able to describe her feelings.

"Another of the general's children, James, was affected somewhat like his father, but not so severely; he would appear about to have a spasm if he remained in the presence of a cat and his friends were obliged to keep them from the room he was in. None of his children inherited this; but it has appeared among his grandchildren of the P. family, who are 'afraid of them.'

"Miss Mary E. Roberdeau partially inherited this antipathy, which here showed itself in another form, occasioning an eruption on the skin, passing off after the cause was removed."

My informant adds: "Very similarly affected was the writer's sister. Although excessively fond of pets, and cats in particular, it has been noticed that after fondling one a most terrific cold in the head would suddenly ensue. She would sneeze time after time, her eyes water profusely, and her face become flushed. The violence would subside after putting the cat away, leaving no trace visible the next morning. It has always been considered a modified form of her great-grandfather's antipathy."

Dr. S., a physician of distinction, writes: "I am not now aware of the presence of a cat when it is not in sight or known to be near, but on some occasions of my life I have been so uncomfortable that I have feared a cat must be in the room, and on those occasions a cat has always been found. This slackening of my instinct is another reason for supposing that my cat fear is not so great as it used to be. I could never make a friend of a man or woman who loved fondling cats, and I have often had to get a patient to banish the cat from the room before I could give my mind to her symptoms.

"My wife reminds me of one occasion, about 1892, when she and I were visiting a stranger. I remarked during the absence of the hostess that I was certain there must be a cat in the room. Eventually a black cat appeared from under the sofa. I have dread, to the production of nausea. The whole subject seems to me disgusting, and I feel almost seasick as I dictate this. I know nothing about the cat odor except the penetrating and horrible smell belonging to all cat excrements, some of which causes stray homeless cats to smell in the same way. I doubt if this odor can be more disgusting to me than to other people."

Dr. W. writes, giving very remarkable instances of her power to detect the presence of cats. She does not smell them. She has at one instance fear, violent palpitations of the heart, flushes, nausea, and pallor, panting respiration. She was until ten years ago unfailingly able to tell at once if an unseen cat was near. She has lost this power.

An absolutely trustworthy witness, Miss C., relates to me this incident: "I want to tell you of a cousin of mine, a woman as strong-minded and self-reliant as anyone I have ever known and apparently afraid of nothing, but with an absolute antipathy to a cat. On one occasion we arrived in Montreal quite late at night, and on reaching the hotel were taken into a very long dining-room, with lights only on the table where we were seated. She suddenly turned ashy pale and exclaimed: 'There is a cat in this room,' and in spite of the waiter assuring her that he had not seen a cat since he had been there and was quite sure there was none, she got paler and paler and trembling all over, continued to say, 'There is, there is a cat here,' and after much searching a cat was found in the corner and at the extreme other end of the room. I have always thought this very strange, but I saw it myself."

A lady in good health and not at all nervous writes: "I dread cats. My bad dreams are always of cats crawling over me. I can, I say it without doubt, tell if a cat is in the room. I do not smell it, nor do I know how I know it. I do not become faint, only I fear and have a creepy sensation."

I should overload my paper if I were to relate in detail the cases in which cats were concealed in order to test the disbelieved capacity to detect them when not in sight and in which the hidden cat was at once known to be near. One or two permit of doubt; others are unassailable.

There are these classes of persons who suffer from cats:

1. Asthmatics—cat asthma.

2. Those who suffer from cat fear, with or without sequent, excessive, emotional manifestations, and only on sight.

3. Those who have the power to be sure an unseen cat is near. Symptoms same as in Class 2, and apt to be extreme.

4. Those of the last class can detect the cat by smell, or may sometimes and not always.

5. Persons who have been able to distinguish the presence of a cat by its smell but cannot any longer do so in this way, yet retain the ability to detect unseen cats.

It is therefore likely that the cat emanations may affect the nervous system through the nasal membrane, although unrecognized as odors.

Why these emanations should, if plainly perceived as due to cats, cause certain symptoms in those who dread cats is readily understood.

The ultimate cause of unreasonable terror of cats I cannot explain.

To be told that a cat is near when none is in the room may occasion the same unpleasant consequences as when the cat is present.

It is, perhaps, worthy of note how many of the victims of cat fear declare that even strange cats seem to have an unusual desire to be near them, to jump on their laps or to follow them.

A CONTRIBUTION TO HEMOPHILIA, WITH SPECIAL REFERENCE TO THE JOINT SYMPTOMS OF THE DISEASE.

By FRANCIS P. KINNICUTT, M.D.,
OF NEW YORK.

The case which forms the basis of this paper is told in perhaps wearisome detail to illustrate the life history of a hemophiliac and to furnish data for a discussion of some of the features of the disease.

The parents and grandparents of the patient, on the paternal side, have been known by me for many years, and every facility has been at hand for the thorough investigation of the patient's ancestry.

L. P., aged sixteen years.

Family History. Paternal side: The father, grandfather, great-grandfather and great-great-grandfather were free from any evidence of hemophiliac disease.

The mother and her direct ancestors, on both sides, for four generations were similarly free.

The grandmother on the paternal side was free from the disease, and was a first cousin of the grandfather on the same side—*i. e.*, the paternal great-grandfather and maternal great-grandmother on the paternal side were brother and sister.

The mother of the patient has borne four children, three boys and one girl. Three of them are alive and exempt from any *evidence* of hemophilia.

Personal History. His mother states that from birth the patient's skin was noticeably thin and of a delicate texture and its color of an ivory whiteness. When he was five months old she noticed a small swelling on his leg, which was also discolored, the result, she believed at the time, of the child knocking his leg against the crib. A little later a "blackish lump" the size of an egg suddenly appeared on his chest, without ascertainable cause, and persisted for many weeks. When two years old the patient began to suffer from severe nose-bleeds, which were finally controlled with much difficulty by plugging the nostrils. From this date until five years of age he was never free for more than a few days from "black-and-blue spots" on various parts

of the body; some of them could be traced to slight injuries; others appeared without known cause.

At five years he began to have attacks of "inflammatory rheumatism," necessitating confinement to bed for two or three weeks in the individual attacks. They evidently were of a similar nature to those occurring later under my observation, and were probably of traumatic (hemophiliac) origin, as the mother states that it was regarded as a curious phenomenon that they were usually preceded by a "bump" of the affected joints.

A nose-bleed at eight years was controlled only after forty-eight hours, and nearly proved fatal. A little later, following a blow on the thigh, the entire limb became greatly swollen and was apparently the seat of a very large extravasation. The following year, accompanying and subsequent to a coryza, there was slight bloody oozing from the nostrils for several weeks.

In the same year the boy suffered from an attack of supposed rheumatism, involving his left hand, which became greatly swollen and discolored; the mother states that it was almost black. Dentition occurred at the normal period and was unattended with hemorrhage, with the exception of a slight oozing from the gums with the irruption of the last teeth. The patient was not vaccinated on account of the fear of bleeding. The diseases of childhood were attended with no unusual symptoms.

The patient was first seen by me in 1897. From this date until his death, seven years later, he was under my observation. My advice was sought for a recurrence of his "rheumatic" trouble. Immediately preceding this date there had been a nasal hemorrhage, only entirely controlled after nineteen days; for the first twenty-four hours it was of a very violent nature.

On examination the patient was found to be of slight physique, with well-developed musculature, to possess a sensitive nervous organism and a bright intellect. The skin was of fine texture and of ivory whiteness. The skin of the face seemed unnaturally thin and transparent, the blue lines of the veins showing through their superficial covering. The examination of the different organs gave entirely negative results. The radial artery at the wrist in pulsation seemed of normal size, and the outlines of the heart showed an organ of normal dimensions. Urinalyses elicited no abnormalities in the secretion. There were several skin areas on both the upper and lower extremities, some of large size, presenting various degrees of discoloration from a nearly black to a yellowish-green hue. The left knee was greatly swollen. The swelling was due to a large intra-articular effusion with little if any into the periarthritic structures. The skin was drawn very tightly over the effusion, but was not reddened or discolored. There was acute pain in the joint, both spontaneous and on movement. The joint symptoms were believed by the mother to be of a rheumatic nature and to have followed a misstep on the stairs.

In view of the previous history of the patient, the arthritic symptoms were regarded by me as of hemophiliac origin and due to intra-articular hemorrhage. The temperature was only moderately elevated (100° to 102°). The arthritic symptoms gradually disappeared, and at the end of a month the joint was quite normal in appearance and its movements were unimpaired.

A similar attack occurred a year later, and on this occasion involved the right knee. In this attack there was discoloration about the joint. Subsequent to the absorption of the effusion the function of the joint was unimpaired.

There were no further arthritic symptoms until 1900, when there was a very severe attack again involving the right knee. The joint was greatly swollen, with extreme tension of the overlying skin and exquisite pain, both spontaneous and on movement, requiring large doses of morphine. The skin was not reddened during the attack, but there was much subsequent discoloration about the joint. Improvement was very gradual and an acute recurrence occurred at the end of a few weeks. There was fever throughout the earlier stage (ten days) of both attacks, the maximum temperature being 103° with a diurnal variation between morning and night of about 1.5°. The patient was practically confined to his bed for eleven months, as a recurrence of the intra-articular effusion developed whenever any attempt was made to place him on his feet. During this period the other knee (the left) was slightly affected on two occasions. There was also one severe attack of hematuria.

Following the above prolonged disability and during the two subsequent years both knee-joints were on several occasions slightly affected, but no severe arthritic attack occurred until 1902. Notwithstanding the frequency and severity of the articular effusions, with their resorption, the function of the joints up to this date remained unimpaired. Occasional nose-bleeds during this interval were rather easily controlled by local applications of adrenalin.

In the summer of 1902, and again in the early autumn, large interstitial hemorrhages occurred into the left upper and lower extremities, in the latter instance involving the whole of the left calf. In October of the same year, shortly following the sudden occurrence of exquisite pain in the right half of the abdomen, the patient presented all the symptoms of grave hemorrhage, syncope, extreme pallor, etc., and a large interstitial hematoma was speedily palpable, occupying nearly the whole of the left abdominal wall. The hemorrhage was deep seated, as no discoloration of the overlying skin followed. Resorption only took place after many weeks.

From 1902 until death in the summer of 1904 there occurred another severe hematuria, an effusion into the left elbow-joint, and a constant succession of effusions into the capsules of both knee-joints, more frequently the left. In none of the joint involvements was the skin reddened. In all the attacks pain was present, both spontaneous and on movement, and there was a rise of temperature, slight in the less severe attacks, as high as 103.5° with the larger effusions. *Pari passu* with the diminution in the swelling, the temperature fell and the spontaneous pain subsided. The pain on movement persisted for very considerable periods.

As a rule the effusion was wholly intracapsular. In a few of the attacks there was also a periarticular infiltration, as shown by the subsequent discoloration about the joint.

Gradually during the last two years of life the signs of a chronic arthritis of the knee-joints developed. There was obvious thickening of the peri-

articular tissues, of the synovial membrane, fringes became palpable, and the character of the crepitus suggested partial destruction of the cartilage of the left knee-joint. Finally, severe contracture and a partial ankylosis of a fibrous nature, of the left knee, developed. There was very considerable atrophy, probably largely from disuse of the muscles related to the joints, especially of the left knee. The articular ends of the bones entering into the structure of the joints seemed enlarged, but as no radiographs were taken, the apparent enlargement may have been due to the thickening of the periarticular tissues.

In February 1904, after walking on his crutches a short distance, and without any appreciable injury, the patient suddenly complained of acute pain in the abdomen, especially in the right lower half. He gradually became blanched, with fluttering pulse, and presented all the symptoms of concealed hemorrhage. When seen by Dr. Draper and Dr. Hance, he lay with knees drawn up and complained of acute pain in the lower portion of the right abdomen. The whole abdomen was distended and rigid; there was marked tenderness on palpation in the right inguinal region, with muscle resistance; no mass could be palpated. Rectal examination was negative. The urine was free from blood. Temperature, 101°; pulse, 120.

During the following week the symptoms continued to be of a very grave nature. The temperature fluctuated between 101° and 103°, and on the seventh day an intra-abdominal tumor could be palpated in the right inguinal region. From this date improvement gradually occurred, and with diminished rigidity of the abdominal walls the intra-abdominal mass was palpable in the lower portion of both inguinal regions and above the symphysis pubis. Resorption gradually occurred, and at the end of six weeks no distinct tumor was palpable. In the summer of 1904 the patient was taken to his home in Ohio, and in July there was a sudden recurrence of acute abdominal pain and all the symptoms of concealed hemorrhage. No blood was passed by the bowel. Syncopal attacks speedily followed and a fatal issue in twenty-four hours from the occurrence of the first symptoms.

No autopsy was obtained.

The case related possesses many points of interest; its congenital, yet not ascertainable, inherited character; the frequency and severity of the arthritic attacks, the involvement of the smaller joints (the hand) on one occasion, the eventual development of permanent structural changes of the joints, and, finally, the occurrence of intra-abdominal hemorrhage and death, probably from this cause.

The hereditary nature of hemophilia was recognized as early as 1784 by Fordyce,[1] and, with continued observations, the mode of its transmission is now well recognized. Briefly, it is as follows:

1. As a rule the daughters of a bleeder father are exempt from evidence of the disease, but transmit it to their male offspring.

2. The sons are also, as a rule, exempt, and do *not* transmit it to their offspring.

3. The daughter of a bleeder father may transmit the disease to a single one, to several or to all of her offspring.

4. Where there are several daughters the capability of transmission to offspring may be confined to a single one, or all the daughters may transmit it.

5. Occasionally there is a direct transmission from father to son through several generations.

6. The disease does not appear in the issue of sons of a bleeder family who are not themselves bleeders.

Following such laws the transmission has been traced through many generations. In the Appleton-Swayne family of Reading, Mass., instances are present in the seventh generation.[2]

In the Clitherow family of Prescot, Lancashire, the transmission has been traced back to 1770,[3] and in two families of Tenna, Switzerland, to 1770, when they united in a common ancestor.[4]

It is reasonable to believe that a *de novo* origin of the disease is possible. The evidence in the literature to this effect is very considerable. Where, as in the case related, four generations of ancestors on both sides have given no evidence of the disease, no other conclusion seems possible.

It is interesting to note that both the patient's father and grandmother on the paternal side were sufferers from diabetes, and that the two families on the paternal side sprang from a common ancestor four generations back.

Joint Affections. As early as 1838 Dubois[5] asserted that the intracapsular effusions in hemophilia were of a hemorrhagic nature. As his views were not based upon aspirations made during life or upon examinations after death, they were not generally accepted. In 1868 Reinert[6] published a case which he believed lent support to Dubois' statement. A year later Assman[7] reported the finding of fluid blood on puncture of a swollen knee in a patient suffering from hemophilia. Legg,[8] in his treatise on *Hemophilia*, published in 1872, wrote that the nature of the joint swelling was as obscure as the rest of the pathology of the disease,

and that he was not acquainted with the record of any examination after death of the joints of a patient who had suffered from the swelling common in hemophilia. The generally accepted view at this period was that the arthritic symptoms of hemophilia, early recognized as characteristic of the disease, were of a rheumatic nature. Since 1872 our knowledge of the pathologic anatomy of these arthropathics has gradually grown. The literature, however, is strangely scanty, and is embraced in the reports of autopsies by Virchow (Lemp's case),[9] by Poncet,[10] Sir William Jenner,[11] König,[12] Sandelin,[13] Tilman,[14] of joints aspirated or opened by Ligorio,[15] in King's College Hospital[16] (incision and autopsy, Legg's case), in the Bristol Royal Infirmary, England (aspiration, Greig Smith and Shaw's case),[17] by Cheyne,[18] by Dufour,[19] Chaves and Speroni,[20] and, finally, in radiographic studies by Sabrazes and Cabannes,[21] by Gocht,[22] by J. E. Shaw,[17] and by Kinnicutt.[23] The majority of these observations are on single cases.

It will be of interest, before considering the conclusions reached from these observations, to review the symptomatology of the joint affections. From a careful study of the literature it is evident that the arthropathics, contrary to the generally accepted belief, may occur in earliest infancy. Pearce[24] reports a case in an infant ten days old, Shaw[25] at seventeen months, Eve[26] at eighteen months, Kinnicutt[23] at three years, and a number of recent observations indicate the not infrequent appearance of joint symptoms between two and five years of age. In the case related the arthritic attacks first occurred at five years; on the other hand, a marked tendency is shown to the gradual cessation of joint effusions, even when they have been of unusual frequency and severity, after the completion of pubescence. The small joints, as a rule, escape. The knee is most often attacked; the elbow, ankle, hip, shoulder, and hand-joints follow in successive frequency. The clinical manifestations vary greatly, and do not seem to be wholly dependent upon the amount of the effusion. The effusion generally reaches its maximum within twenty-four hours; occasionally subsides very rapidly, but more frequently after ten to fourteen days, leaving an unimpaired function of the joint in many instances. The process may be repeated almost indefinitely, and often for a long period all evidence of structural

joint damage is absent. There are occasional instances where complete recovery has not followed even a first attack. In one of Sadler's[27] cases the affected joint was never normal after the first attack at three years of age. In another of his cases permanent deformity was present at the age of ten years.

The overlying skin may be reddened or it may preserve its normal color during the period of effusion. In two personal cases observed in the past year repeated effusions were unaccompied with any change in the color of the skin. In such instances the joint affection has often been mistaken for " white swelling." Discoloration not infrequently has been noted *about* the joint, indicative of an associated extracapsular hemorrhage. Pain, often of an exquisite nature, spontaneous and on movement, accompanies the swelling, as a rule. In the case related it was controlled only by very large doses of morphine. In the absence of visible signs of inflammation and in the presence of extreme tension in many of the attacks in this case, the pain was believed to be due to the stretching or compression of the synovial nerve filaments. Occasionally the pain radiates from the joint, following the course of the nerves (Hamilton's case[28]). The symptom usually subsides *pari passu* with the resorption of the effusion. Occasionally the pain disappears within a few hours, even with the persistence of the swelling (Gocht's case[22]). Exceptional instances have been reported where even large effusions have been unaccompanied with pain (König's case[12]). Fever usually accompanies the attack, maximum temperatures in individual cases of 100° and 103.5° being noted.

Although cases in which studies of the joint affections through incision, aspiration, and by radiographs during life and of the structures after death have been few and limited in the case of individual observers to single instances, with the exception of König's three cases, it may be asserted with approximate certainty that the arthritic attacks and subsequent structural changes are dependent upon a succession of intracapsular hemorrhages.

It was possible for König[12] to study the pathologic processes in their various stages, and his observations have been confirmed by other observers. In the first stage there is a simple hemarthrosis. The joint is filled with fluid or coagulated blood; the synovia are injected, hyperemic and covered with streaks, hemorrhagic clots.

In the earlier attacks no further change presumably occurs. The blood is speedily absorbed and there is complete recovery. In the second stage, usually present after numerous effusions, the joint contains more or less bloody or pure serum. The synovial membrane is slightly thickened, presenting numerous thickly-set, brownish-stained villi or fringes. The cartilages have lost their white color and smoothness. Masses of fibrin encroach upon them, showing a tendency to the formation of connective tissue, possible forerunners of adhesions. Erosions of the cartilages are also observed, especially at points where the accumulations of fibrin have occurred.

The third stage is that of deformity, which, in varying degree, I believe to be the inevitable result of protracted hemophiliac arthritis—*i. e.*, frequently repeated attacks over a long period. In this stage ankylosis of varying degree, sometimes complete, usually of a fibrous character, is present. The capsule is greatly thickened; there is greater or less destruction of the cartilages; the joint cavity is filled with fibrinous deposits, more or less adherent; subluxation has been observed, and, finally, changes in the bones entering into the structure of the joint have been described.

Observations in regard to such changes are conflicting. Poillet,[29] on the authority of Sandelin, asserts that there is marked atrophy of the articular ends. Gocht's [22] radiographs apparently show that the bones are porous and less voluminous. In Sabrazes' and Cabannes'[21] radiographs of a protracted case, with moderate ankylosis, the articular ends of the bones are seemingly intact; on the contrary, Bowlby[30] observed in three cases of protracted hemophiliac arthritis, during life, enlargement of the articular ends with projecting nodules of bone; and studies of hemophiliac joints in the museum of St. Bartholomew's Hospital [31] show lips of new bone at the edges of the condyles of the femur covered with nodular masses of cartilage. In the case related in the present paper examination during life showed apparent enlargement of the articular ends. In the second case observed during the past year with moderate ankylosis radiographs gave a less clear definition of the diaphysial end of the femur related to the affected joint, the right, than of the left femur. The density of the bony tissue seemed to be increased.

They also indicated the presence of a turbid intracapsular effusion, presumably blood, or of a blood clot. The radiographs were taken three weeks after the occurrence of an effusion. The arthritic attacks in this case had not been of sufficient frequency, presumably, to produce marked structural changes in the articular ends of the bones.

In view of these observations a justifiable conclusion would seem to be that both hypertrophy and atrophy of the articular bony structures occur in the late periods of hemophiliac arthropathies, possibly representing different stages of the pathologic process.

Bowlby[32] regards the changes as analogous in most respects to those occurring in osteoarthritis. Goldthwait[33] believes that *atrophic*, rather than hypertrophic, changes are characteristic of true osteoarthritis (arthritis deformans).

It has been stated earlier that in patients surviving the age of pubescence joint effusions become less frequent or do not occur. Gocht[22] suggests that an explanation may be found in the anatomic lesions. Where the joint is filled with more or less organized fibrous products a diminution in the frequency or severity of hemorrhage is to be expected. Another reason may be found in a diminution in the hemorrhagic tendency in hemophiliacs with advancing years.

The lesions of both the second and third stages have been mistaken not infrequently for those of tuberculous arthritis and arthritis deformans, respectively. A differentiation by physical signs obviously may be often impossible.

In the second case referred to in this paper a joint lesion was believed by orthopedic surgeons to be of a tuberculous nature until a nearly fatal surface hemorrhage (extraction of tooth) led to a more minute inquiry into the history of the patient.

König,[12] in one of his cases, opened the joint on the supposition that the disease was of a tuberculous nature. A fatal issue followed from hemorrhage. J. E. Summers[34] reports a similar case with a fatal issue. Cheyne[18] operated on a case of supposed arthritis deformans with nearly fatal issue from hemorrhage. It was subsequently discovered that the patient was a hemophiliac, and later other joints were affected.

In the literature I have been able to find a number of instances

where in families of bleeders the male members have severally exhibited joint affections without evidence of other bleeding, and surface bleeding with exemption from arthritic symptoms during the early years of life. In the history of a bleeder family reported by Sadler[27] this is clearly shown. The observation is an important one from a diagnostic standpoint.

The practical deduction from the above observations is that in joint affections bearing a resemblance to tuberculous disease in infancy and childhood the family history, as well as the personal history, should be studied carefully previous to operative treatment. The tuberculin test in a hemophiliac is not without danger from injury by the needle.

Before concluding the study of the joint affections a word should be said in regard to the origin of the hemarthroses. It would seem justifiable to conclude from the clinical histories of a large number of cases that they may be both of spontaneous and traumatic origin, as is the case in the bleeding from other tissues of the body, in hemophilics.

An explanation of the frequent recurrence of hemorrhage in a single joint is suggested by the hyperplasia of the richly vascular synovia. The hyperplastic tissue once developed would permit of nipping from very slight causes.

Peritoneal hemorrhage in hemophilia must be of the rarest occurrence. In the voluminous literature which I have consulted I have been unable to find an instance, unless Lemp's case may be regarded as an example of this kind. The physical signs of an intraperitoneal tumor were apparently present during life, associated with a hematoma of the upper portion of the thigh; and at autopsy a sausage-shaped tumor was found in the iliac fossa, whose composition was shown by microscopic examination to be of altered blood. In the case related in this paper the physical signs of a hemorrhage of this origin were demonstrative, and it is probable that the fatal issue was due to bleeding from a similar source. The hemorrhage may have been either spontaneous or due to some slight and unrecognized traumatism, such as a strain in the use of the patient's crutches.

It is presumable that the bleeding was from omental tissue, the blood gravitating to the most dependent portions of the abdomen.

Treatment. The treatment of the hemorrhage in hemophilia, at the best, is unsatisfactory, and often is ineffectual. A great variety of methods and drugs have been employed from time to time, only gradually to be discarded.

Legg,[35] in his latest publication on hemophilia, reiterates an opinion previously expressed by him[36] that "one of the most satisfactory ways of treating the bleedings is to leave them to themselves." He adds that "after they have lasted for some days and the patient is blanched and exsanguine they cease and the patient gradually recovers." Such action, or lack of action, requires greater courage than is commonly possessed by the medical attendant.

I shall only refer to therapeutic measures, which, comparatively lately, have been employed, and which have been regarded favorably. Drugs which act as "physiologic styptics" when applied locally, and which also possess the power of increasing the coagulability of the blood when administered internally, may properly be considered as furnishing a rational therapeusis in hemophilia.

A physiologic styptic, using Professor Wright's term, differs essentially in its action from that of such styptics as tannic acid, the salts of the heavy metals, alcohol, the actual cautery, etc., which produce their effect by a coagulation or a disintegrating process, with possible subsequent eschar formation or an inflammation of varying degree. The physiologic styptic possesses an elective affinity for the blood itself, and is inert when brought in contact with other tissues. In the lime salts these properties are found. In his investigations on "Increasing and Diminishing the Coagulability of the Blood,"[37] Wright was able to demonstrate by experiments in healthy human beings and in hemophiliacs that the coagulation time of unmixed blood could be reduced more than one-half by the addition to it of one-sixth volume of a 1 per cent. solution of calcium chlorid; also, that a similar result could be obtained in hemophiliacs by the administration of calcium chlorid in doses of 2 grams (30 grains), twice daily, the effect being appreciable within a few hours from the beginning of treatment. His investigations further showed that the continued administration of large doses of calcium chlorid for four or five successive days was ineffectual in maintaining an increased coagulability of the blood; that its temporary discon-

tinuance resulted in an *increase* in the coagulability, the maximum being reached in twenty-four hours, an effect presumably due to the elimination of an *excess* of the lime salt. In the subsequent forty-eight hours the coagulation time remained at about the same level, only to diminish again one-half in the short period of eight hours after the readministration of 2 grams of calcium chlorid.

The accelerating effect of carbonic dioxide gas upon blood coagulation also suggested to Wright the employment of the gas in the treatment of hemorrhage in hemophilia.[38] In the surface bleeding the stream of gas is gently turned upon the affected surface, inhalation being unnecessary. The result of such applications in the epistaxis and buccal hemorrhages of hemophilia has been excellent. In concealed hemorrhage the *inhalation* of the gas has been used with success. The gas should be freely mixed with ordinary air, as asphyxia in *any* degree is to be avoided. An anoxyhemic condition of the blood induces a diminished coagulability.

Finally, Wright,[39] basing his therapeusis on the diminution in the white blood cells, and especially the polynuclear elements in hemophilia, has employed solutions of cell nucleoalbumins for local applications. He reasons that in the deficiency of white corpuscles the blood lacks the cellular elements which contribute the nucleoalbuminous elements to the formation of fibrin. The addition of nucleoalbumins is therefore essential to the formation of a sound clot.

Lachan Grant[40] has very recently reported a case of obstinate bleeding in a hemophiliac successfully treated by the internal administration of 2½ grains of ovarian extract thrice daily. While the hemostatic action of the ovarian extract cannot be regarded as demonstrated in this instance, the theory which formed the basis of its administration is both ingenious and of interest. Good results have also been claimed recently[41] from the use of thyroid extract. The use of gelatin preparations, either locally or by subcutaneous injections, has proved as disappointing in hemophilia as in other conditions where an increased coagulability of the blood is desirable.

Among the therapeutic agents affecting the circulation of the blood through their action, either upon the vessel walls or the

vasomotor centres, or both, chloral hydrate and adrenal preparations have been found of distinct value as local applications in hemophilia.

To summarize the present views of the most efficient therapeusis of hemophilia:

1. The internal administration of the lime salts, especially of calcium chlorid, in doses of 2 grams (30 grains), twice or thrice daily. Its continued use should be interrupted every two or three days by a period of twenty-four hours. The salt is soluble in 1.5 parts of water, and is well borne by the stomach.

2. The application of solutions of the same salt, with compression, for accessible surface bleedings. Aqueous solutions of $\frac{1}{2}$ per cent. are efficient. Another convenient mode of employment is in the form of a finely powdered chalk mixed with $\frac{1}{2}$ per cent. solution of the calcium chlorid. The less soluble lime salts, such as calcium phosphate, are equally efficient for local application.

3. The use of a combination of $\frac{1}{2}$ per cent. solution of calcium chlorid and one-sixth volume of a solution of nucleoalbumin for local application. The nucleoalbumin can be obtained from aqueous extracts of various cellular tissues—testicle, thymus, thyroid, ovary, etc. If the prepared extracts are not available a supply may be procured readily by mincing any of these tissues in a weak alkaline solution (1:500 solution carbonate of soda) and filtering through gauze after a few minutes.

4. The application of a stream of carbonic acid gas to the bleeding surface in accessible hemorrhage. Its inhalation, freely mixed with ordinary air or oxygen, in concealed hemorrhage.

5. The use of 4 per cent. solutions of cocaine hydrate for surface bleedings, and also of adrenalin (1:1000) with compression.

My personal clinical experience in the treatment of hemophilia has shown me the value of the therapeusis described for accessible hemorrhage. At times in the history of the case related I was convinced of the efficiency of calcium chlorid administered internally. I have been equally convinced of its value in the hemorrhages of some other constitutional diseases.

The marked increase in the coagulability of blood following its internal administration admits of demonstration, and, although

its effect in hemophilia unquestionably is often disappointing, possibly through ignorance of the proper mode of its employment, a general consensus of opinion at the present time gives it a high value in the treatment of the disease.

Bibliography.

1. Fragmenta Chirurgica et Medica, London, 1784, p. 41.
2. Practice of Medicine, Osler, 1901, p. 819.
3. St. Bartholomew's Hospital Reports, 1881, vol. xvii. p. 304.
4. Ibid., p. 306.
5. Gaz. méd. de Paris, 1838, p. 43.
6. Ueber Haemophilie, Diss. Inaug., Göttingen, 1869; Abstr. Jahresbericht, Virchow-Hirsch, 1869, ii., S. 268.
7. Die Haemophilie, Diss. Inaug., Berlin. 1869; Abstr. ibid.
8. A Treatise on Haemophilia, London, 1872, p. 101.
9. De Haemophilie Nonnulla, Diss. Inaug., Berlin, 1857; see also, Deutsch. Klinik, 1859 Nr. 23.
10. Lyon méd., 1871, vol. viii. p. 785.
11. Medical Times and Gazette, 1876, vol. ii. p. 610.
12. Volkmann's Sammlung klinische Vorträge: Chir., 1892, n. f. 36.
13. Quoted by Piollet, Gaz. des hôp., Paris, 1902, vol. lxxv., 385.
14. Deutsche Aerzte-Zeitung, 1900, S. 421.
15. Settimana med. dello Sperimentale, 1898, lii., p. 445.
16. St. Bartholomew's Hospital Reports, 1881, vol. xvii.p. 310.
17. Bristol Medico-Chirurgical Journ., 1897, vol. xv. p. 240.
18. Clinical Journal, London, 1900–1901, vol. xvii. p. 402.
19. Clinique Bruxelles, 1903, xvii. p. 893.
20. Revista de la Sociedad Medica Argentina, 1903, xi., 297.
21. Gaz. heb. des sc. méd. de Bordeaux, 1898, xix. p. 510.
22. Arch. f. klin. Chir., 1899, lix., S. 482.
23. Personally observed during the past year and briefly noted in this paper.
24. Brit. Med. Journ., 1898, i. p. 1135.
25. Bristol Medico-Chirurgical Journ., 1897, xv. p. 244.
26. Lancet, London, 1889, ii. p. 1002.
27. Birmingham Med. Review, 1898, vol. xliv. p. 45; ibid., 1902, vol. lii. pp. 354–358.
28. Medical Record, N. Y., 1891, xl., 617.
29. Gaz. des hôp., Paris, 1902, lxxv., 385.
30. St. Bartholomew's Hospital Reports, 1890, vol. xxvi. pp. 77–82.
31. Ibid., pp. 80, 81.
32. Ibid., pp. 81, 82.
33. Boston Medical and Surgical Journ., 1904, cli. p. 529.
34. Medical Record, N. Y., 1896, xlix. p. 336.
35. A System of Medicine. Allbutt, vol. v. p. 554.
36. St. Bartholomew's Hospital Reports, 1881, vol. xvii. p. 313.
37. Brit. Med. Journ., 1894, ii. pp. 57–61.
38. Ibid., pp. 58, 59.
39. Lancet, London, 1896, i. pp. 153–155; ibid., 1893, i. p. 435.
40. Ibid., 1904, ii. pp. 1279–1280.
41. Brit. Med Journ., 1900, ii. p. 1375.

SOME PHASES OF THE NEUROTIC HEART.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK CITY.

To my mind there are few chapters pertaining to general medicine less well understood practically than the recognition and judicious treatment of nervous disorders of the heart. I would assign several reasons for my belief in this statement, which is the result of numerous continued observations dating back through many years. First, many of our inquiries to-day, especially those we are apt to regard as more accurate and complete, are made in dispensaries and hospitals, particularly the latter. Usually we regard a case as insufficient and unsatisfactory where an autopsy has not completed our record, or an evident and radical cure been established. In instances where the patient has been more or less of a sufferer during many years, and never seems entirely well, we have reasonable doubts, frequently, as to the accuracy of our diagnosis. This depends upon the fact that, seen at different times and under various conditions, the patient varies a great deal as to symptoms, and also, in measured degree, as to physical signs which are recognized. The patients who usually afford us the most satisfaction in the sense that we feel, as far as may be, we have mastered the correct interpretation of their suffering, are seen in private practice. In hospital cases we find many causes which lead to error in final judgment. For example, there is the previous history in which certain details are almost always lacking, because we cannot get at all the home habits and influences which have so much importance in fixing our opinion; in the hospital the nature of the case and treatment are not invariably the best we feel we could advise or urge. And yet we are really so handicapped by

conditions of nursing, food, surroundings, arrangements, regulations, rules, etc., over which we can really have but partial control, that we become hesitating and uncertain at times about whatever is at all difficult and obscure. Again, often patients have left hospital, where they have been under observation only a few weeks or months. If they survive, they frequently pass from our knowledge entirely, and we are not at all cognizant of the future developments of the case. Even in the hospital, and when death occurs, an autopsy may not be obtained, and even if the autopsy is made very carefully, there are many points connected with the findings from the point of view of neurology of the heart, forcibly almost, which remain incomplete and unsolved. Finally, modern life, with all its many cares, worries, obligations of increasing number, has augmented the neurotic hearts many, many times, and yet rarely do we meet simple cases of the kind. Usually, there is evidently present or there is reasonable doubt as to the coexistence of vascular or muscular changes in the nervously affected heart. Thus we see in advance how difficult and multiple the problem is when we wish fully to compass the so-called neurotic heart in all its detail and significance. As to its importance, particularly from the point of view of individual health and happiness, there can be no doubt. Already I have had to do with many who had been a source of misery to themselves and others by reason of a faulty diagnosis and prognosis on the part of the physician. This could be remedied only with greater care, sympathy and knowledge. I hope what I shall be able further to say may prove useful to those who, like myself, have felt the need of more light on this interesting and important subject. The cases of neurotic heart are, in broad terms, of four kinds: First, those where there are general evidences of a condition of neurasthenia or hysteria, or other well-defined nervous disease. Second, those in which there is manifestly organic change of heart or vessels. Third, those where there is present a disease of stomach, bowels, pelvic trouble, etc., of which the cardiac disorder is an apparent reflex. Fourth, those cases in which the causes of neurotic heart are various, often not perfectly clear, and those also where the concomitant trouble is as much effect, probably, as cause of neurotic heart. It is my intention to refer particularly in

this paper to the latter class. I was called only a few days ago to see the following case:

A lady, married, aged fifty-two years, with one child grown and healthy. This patient has suffered for several years from symptoms of heart disorder, consisting essentially in palpitation, a feeling of goneness around the heart, nervous dread of impending, sudden illness from heart disease. Five years ago she had what appeared to be a complete plugging of radial artery, probably due to a thrombus. Since that time she has had several attacks of temporary loss of consciousness without twitchings, foam at mouth or biting of tongue. She suffers from atonic dyspepsia frequently, which is generally occasioned by errors of diet. Examination of heart does not reveal any organic changes. The pulse is regular with increased tension to palpation, even at times when she complains of great weakness. The urine is shown to be normal. Whiskey and ammonia suit her best, among remedies, at the time of her faint attacks. Latterly, she has taken every night 10 grains of sodium bromide to ward off attack of unconsciousness, and for two years she has had none. The frequent use of carminatives (tinctura cardamomi comp.), supported with cheery and hopeful affirmations, have given renewed well-being rapidly, when she was visibly affected from distressing heart symptoms (weight, oppression, weak feeling). Her flow is now irregular (every two or three months), not profuse, and unaccompanied with pain. She is generally nervous. The diagnosis in this case was neurotic heart accompanied with dyspepsia. The attacks of unconsciousness are due to stomach and heart reacting upon one another. When the patient is careful of her diet she gradually recovers and has only slight symptoms from heart. Gentle massage, a warm inland resort and a mild alkaline water to drink are counselled. A sojourn at Homburg seems desirable, but she prefers Aix for the summer, by reason of another's cure, who is nearly related.

A young physician came under my care some years ago suffering from mental depression, occasioned by a diagnosis of heart disease made by a prominent practitioner. His local symptoms pointing to cardiac disorder were essentially slight; dyspnœa at times, palpitation, uneasiness and weight in precordial region. On physical

examination a soft, blowing systolic murmur was discovered at the apex, and it was thought due to cardiac relaxation or slight dilatation, possibly. Despite the fact he was passed as a good subject with no heart disease by a well-known life insurance company. At times he suffered from local eczema of hands and eyelids. This was cured with local treatment, apparently, and his cardiac symptoms relieved after a time with coca, guarana, and cactus. At times this patient suffered from mental depression and choking sensations in the throat, which seemed of hysteric nature.

Mrs. A., who called on me in January, 1904, complains of a weak heart. She is a widow, aged forty-eight years; has had la grippe every winter for several years. Fourteen years ago was laid up with an acute attack of rheumatism; no pelvic trouble at present, but some years ago had ovaries and uterus removed for uterine fibroid; temperature normal; urine normal; moderate secondary anemia. Examination of heart negative, except for weak action; pulse regular, with diminished tension. A combination of glycerophosphates of lime and soda with kola and daily massage was of service. Later, the hypophosphites, with iron, manganese, and strychnin, were taken, but the heart still remained weak and the anemia unchanged. In this instance I believe the removal of the uterus and appendages was the underlying cause of nervous disorder of the heart. By suppression of coffee, taken daily several times, no doubt the heart seemed to gain strength and the feeling of weakness to disappear for a while. What is frequently true, and was in this instance, as the heart gained in strength a slight blowing murmur was audible at the apex.

In the case of a young man who had grown rapidly, and who had an attack of pneumonia three years previously, there was complaint of heart weakness. Still, he could ride, row, walk fast, play polo and not feel notably unpleasant effects as an immediate result. He was equipped mentally over and above the great number of men of his age, and worked hard and assiduously as a lawyer. Physical examination of heart showed diminished force, and the pulse was somewhat irregular and of low tension. He had a moderate secondary anemia, and complained often of feeling tired. Iron and other tonics, good food and out-door exercise did not

notably improve the weak feeling at the heart. After a time he disappeared from observation. Here again the weak heart action and secondary anemia seemed to me mainly of nervous origin.

In some of these cases patients may suffer very much from palpitation, and this may come on suddenly, and apparently without provocation. Again, the throbbing and increased intensity and rapidity of heart beats may not be appreciable. In many instances notable physical exertion will not give rise to painful palpitation, although to this rule there are not infrequent exceptions. Undue and prolonged mental effort or lack of proper and sufficient sleep is a very customary source of cardial palpitation.

It is rare to encounter marked slowness of pulse in purely nervous cases of heart disease, and usually when bradycardia is pronounced we must look for organic changes either within or outside of the heart.

The pathology of these cases is at times difficult to determine accurately, and of course many times we are compelled to fall back upon mere theory or speculation to explain symptoms. To-day the latest physiology would place the seat of cardiac automatic action in the muscle cells of the heart, and therefore when these cells are deranged or altered we cannot but appreciate to what degree the cardiac force and movements may be affected. Singular to say, however, that in the simple nervous troubles of the heart digitalis is of little value, and tends rather to increase than to diminish functional disturbance. Inorganic or pseudoangina attacks are not difficult to determine in young people of marked hereditary or acquired nervous constitution. And where there have been overwork, excesses, stomachal derangements, combined or not with anemia, or a marked tendency to rheumatism or gout, the diagnosis is relatively easy. Likewise, if alcohol or tobacco, tea, and coffee have been immoderately used, we can easily in most instances reach a satisfactory and correct conclusion. But in many instances in which we have to do with anginous attacks of men or women past middle life already, with evidences of previous heart disease or arteriosclerotic changes, our anxieties are great and can only be relieved with the passage of time and the future development and outcome of the case.

In the case of a friend I was called to see two years ago, I was very much alarmed about his condition when I first saw him. He was suffering from considerable precordial pain and anxiety, his face was pale and anxious, and his movements distressed and painful. He complained constantly of inability to breathe. His heart was enlarged, with a marked, direct, and diastolic murmur at the aortic orifice; the pulse was frequent and tense. The patient was a dyspeptic, and indulged freely in tobacco. His diet was improperly regulated. He was relieved with frequent doses of nitroglycerin, digitalis, strychnin, and atropin. Two years have elapsed, and he has had no severe return, so far as I know, of what seemed at first to be true angina pectoris, and which I now regard as an accidental determination in a case of chronic cardial disorder. Witness a case of another friend and patient of sixty years, who was of somewhat full plethoric habit, and who had a very nervous temperament, and was markedly lithemic. His habits were exemplary. He did not use tobacco or alcohol; no syphilis or malaria. He was careful as to his diet. He worried increasingly about business matters, although his position was a good one, and the work not immoderate. He had two prolonged summer rests. His heart was seemingly normal, showed no increased size, and no abnormal murmurs. His pulse was as a rule regular and of good force, yet, from time to time, and with increasing frequency, he suffered from attacks of angina pectoris, which gradually became more and more distressing. He felt such intense anguish at times that he thought he was surely going to die, and the perspiration stood out in beads on his forehead during his attacks. Hypodermics of morphin failed finally to relieve his seizures, and nitroglycerin and strychnin could not prevent them. Finally, he had acute delirium in one of his attacks, and died from a failing heart, despite all efforts made in his behalf. In this case autopsy showed sufficient signs of cardiac disease to render it at least probable that they gave a correct explanation of the distressing attacks of angina pectoris during life.

More or less pain and dyspnea in connection with organic disease of the heart is, as we know, very frequent. Notably these symptoms are increased with physical exertion. They often return

periodically, especially during the night, and when no physical exertion has taken place for some hours. In some instances, especially where there is greater dyspnea and less pain, we are inclined to believe the symptoms may be of uremic origin, so called. If the urine be small in quantity and the amount of urea excreted also slight, and if cardiac tonics are apparently of little use, and there is no pronounced heart disease, our opinion often seems warranted. In some such instances it seems as though a combined moderate degeneration of heart and arteries was the best explanation we could give. Finally, however, we should not lose sight of the nervous controlling influence of the heart. If with the difficulty of breathing and pain we have increased frequency of pulse, it seems as though the accelerator nerves of the heart had been unduly stimulated by some toxins formed within the economy, and not properly eliminated, through faulty metabolism. Again, where marked slowness of the pulse is present we feel confident that the inhibitory influence of the vagus is unduly exercised. As regards the causation, we are often obliged to recur to what at best is largely problematical, and rarely, if ever, wholly satisfactory. In one case of a professional man whom I have watched closely for a long period, the slightest emotion will cause very marked palpitation, with a sense of oppression. The heart beats at these times very rapidly and often irregularly. Not only that, but there are also occasional intermittences in heart beats and pulse, which are both subjective and objective. The dyspnea, which comes after any sudden annoyance, care, worry, or unpleasant excitement of any sort, will also occur suddenly and at frequent intervals, and when patient is at perfect rest. It seems quite independent of food and drink. The latter, indeed, have been most carefully regulated. Prolonged rest, out-door life, and freedom from ordinary cares of life will improve the condition very much for the while, but return to previous conditions where little troubles daily arise, and very soon the patient suffers from his cardiac symptoms. With the palpitation and dyspnea there is often a sinking sensation at the heart and a general feeling of prostration. The feeling of acute pain in the precordial region has very rarely been felt, and then only for a short time. In this case moderate, even very active, exercise out-of-doors may be,

and is, indulged in with marked benefit. One exception is tennis, which seems to take away breath completely, and patient very soon suffers very much from previous symptoms. Golf, riding, and rowing are freely indulged in, and only with good effects. The urine is usually light colored, in large quantity, and of low specific gravity. The heart has shown some dilatation for years, never growing worse, never getting smaller. There is at times a soft blowing murmur at the apex. The pulsation in the arteries of the neck is at times very marked, and the internal jugulars are readily dilated and swollen. Rarely does this patient suffer from marked dyspeptic symptoms. The bowels are regular, and the sleep quiet. Different remedies have been used at different times, some with good effect, others apparently inert. When taken for several weeks the glycerophosphates have certainly been useful. As a wonderful temporary stimulant, nothing equals the good effect of the best coca preparation. In winter if cod-liver oil and the hypophosphites be taken for several weeks, with improved nutrition, the cardiac nerves are evidently under better control. In these cases of neurotic heart the quantity and character of the urine vary considerably. Usually it is small or large in amount, of low specific gravity, with small urea elimination, and rarely contains a trace of albumin and a few casts. The latter observed facts are shown frequently, as we know, independently of nervous symptoms in many people otherwise healthy who have passed the meridian of life. Again, I have often seen urine of high specific gravity, moderate or small in quantity, with large urea output, upon cooling, throwing down a large deposit of pink urates or red crystals of uric acid. What is also to be noted is the occasional passage from one condition of urine to the other, and without adequate cause for the change. The urine is often passed very frequently, day and night, and thus causes annoyance. Sometimes frequent urination is only of daily occurrence; at night the patient is free from annoyance.

A maiden lady, aged forty-eight years, came to consult me on account of weakness and palpitation of heart. She is a clerk in a trust company. She is overworked, and in addition suffers from "nagging" of a man whose housekeeper she is, and from loneliness. Her menses are still regular, but rather profuse. She is con-

stipated; suffers from dyspepsia caused by worry and rapid eating; urinates frequently and in large quantity; no fever, no malaria, no diseases latterly; operation for hemorrhoids ten years ago; mother died of uterine cancer, aged fifty-two years; father of heart disease at seventy-five years. Her flesh has increased latterly and she walks very little. When she comes up stairs, much out of breath. Occasionally vague pains in limbs or joints are relieved in a few days with salicin. She does not eat sweets or starches. Examination of heart shows it to be normal; no murmurs; urine, forty ounces in twenty-four hours; specific gravity, 1020; no albumin, no sugar; light straw color; no deposit. Improved upon strychnin, ammonia, and lavender. Glauber's salts every evening kept her bowels in good condition, and when occasional rheumatic (?) pains occurred salicin (10 grains once a day) very soon relieved her.

The following case presents several points of interest: Young man, nineteen years old, has acne simplex; suffers from fainting attacks with almost, if not complete, loss of consciousness. Last attack took place in a crowded place, where there was bad air. Physical examination of heart shows slight thrill at apex, slight cardiac enlargement. First sound not well defined; second aortic sound not accentuated, second pulmonic slightly so; no murmurs; impulse not strong; apex not distinctly visible or palpable, apparently in fourth space near nipple line; pulse depressible. No dilatation of stomach; nevertheless musical sound seemingly proceeding from the stomach with cardiac systole; spleen large; chest negative, although coughs a little; tongue broad and flabby; eats too much and too many things at meals; does not feel worse for physical exertion; feels well after cold sponge bath. Patient was ordered elixir strychnin, pepsin, and bismuth; small doses of creosote and elixir pepsin; regulate diet and exercise; continued care and watching. The diagnosis was hypertrophous dilatation of heart, with a condition of gastric catarrh caused by injudicious eating.

In this case I have no doubt the nervous involvement of the heart would account, in part at least, for attacks of unconsciousness. Of course, I do not make light of other conditions present.

For many years I have had under my professional care a lawyer, now forty-five years of age, bachelor. At different times he has

been a sufferer from obstinate constipation, flatulent dyspepsia, and vague pains of an ambulant character, now fixed over coccyx or ischion, again in region of prostate, over appendical region, or in chest. At times he is a sufferer from neuralgic headaches. All sorts of theories have been invoked at different times to explain his sufferings; malaria, gout, neurasthenia, faulty metabolism, overwork, imprudences of diet, etc., have been sufficiently explanatory at times, and then utterly failed. His urine has shown persistent oxaluria and occasionally a trace of albumin. Latterly his most prominent, unpleasant, or even painful feelings have been connected with his heart. Marked palpitations, gone or weak sensations in stomachal and precordial areas are very evident. The heart is often rapid, tumultuous in its movements. Both aortic and pulmonic second sounds are accentuated. There is visible and forcible uplifting of chest wall at each cardiac systole. At times a blowing soft murmur is heard at apex accompanying the cardiac systole, which also occasions a musical bruit passing in the stomach no doubt, and caused by fluid and gas in a somewhat dilated organ. The ascending and transverse colon is often also evidently distended with gas. Owing to persistent pain at one time below the right costal margin, it was thought that an old adhesion, possibly perityphlitic, might explain numerous conditions which then were interpreted, in part at least, as being of reflex origin. The main indications now being followed are regulated diet, diminished work, prolonged vacations, hepatic stimulants or correctives, and nervous sedatives. During the past few weeks all symptoms have been dormant for a time, and the heart itself more quiet, despite the fact that very marked oxaluria persists.

The treatment of these various phenomena of nervous heart is often puzzling and at times disheartening. At other times we may get rapidly beneficial effects with simple and obvious rational treatment. The good effects are not apt to be permanent, unfortunately, and frequently with little or no adequate cause the patient may again become as great a sufferer as previous to treatment. Indeed, such patients, from continuous suffering and apprehension, may become hypochondriacal, and are then a source of annoyance, trouble, and anxiety to friends and relatives. Finally, however,

as nothing very serious occurs and as life survives, and despite complaints of cardiac flutterings and throbbings, insomnia and cold, chilly extremities, lack of circulation, and expressions of nerve weakness and general depression, mental and bodily, real sympathy from others is as a rule exhausted, and these patients are regarded as confirmed invalids, with innocent and much exaggerated symptoms. Proper, sufficient alvine evacuations are most essential to permanent well-being. To attain this at times is almost impossible, and we are obliged frequently to modify habits and recur to fresh prescriptions. Again, after much trouble and research we usually find some drug or combination which meets the individual requirement in this respect. Some preparation of aloes (preferably aloin) and the sulphate of soda in hot water at bed-time have been found very useful by me. The diet of course should be regulated, and sugars and starches reduced to a minimum. Whenever there is suspicion of rheumatic or gouty condition, so called, the most valuable remedy, and the one with fewest objectionable features, is salicin; sometimes a short course of it will be markedly beneficial. Massage treatment made use of daily is often largely instrumental in helping such patients toward a cure. The different preparations of ammonia, notably the aromatic spirits and the valerianate, are quieting and useful whenever the nervous symptoms are specially annoying and threatening. If the concomitant organic cardiac changes are marked, small doses of digitalis and nitroglycerin, combined and frequently repeated, work wonders occasionally. Whenever we have to do with true angina pectoris, as subsequent events prove to be the case, no medicine or treatment will cure, or even appreciably relieve. At times strychnin in moderate doses, and combined with pepsin and bismuth, has appeared to me useful in several instances. The use of iron for the condition of secondary anemia has seemed to me almost inert, and the blood condition, whatever the precise cause of its impairment in lowered hemoglobin, specific gravity and color index, and moderate increase of leukocytes, has not improved. Subsequently, in one of my cases where the nerve tone was distinctly improved after months of care and treatment, the blood showed a decided increase in the amount of coloring matter and in the number of red corpuscles, an improved

character of the latter, and a normal number and differential count of leukocytes. At the same time the urine analysis showed improvement by reason of a somewhat larger daily amount, a corresponding gravity (1015), and a normal excretion of urea. The favorable progress in this instance was fairly attributable to rest, massage, regulated diet, giving up coffee, and the use of valerianate of ammonia.

The evidences of slight cardiac enlargement, with or without apparent dilatation of the cavities, has remained about, if not wholly, the same during months and years of observation. I believe in some instances we obtain permanent good effects from the prolonged use of the glycerophosphates of lime and soda, combined or not with kola and calisaya. No drug has the same value at times in the control of the neurotic heart as coca. The great difficulty is to obtain an officinal preparation which has any real value. This depends upon several causes: first, the wrong leaf is sometimes used; it is gathered at the wrong season, when it is relatively inert, and does not contain much or scarcely any of the tonic alkaloids of coca. The coca leaf does not bear transportation from its native clime after being gathered, and if this is done the tonic alkaloids which it contains become changed and worthless medicinally as a nerve tonic. For these reasons, most unfortunately, if we wish to give our patients the benefit derived from coca, we are obliged to recur to the use of one or other of proprietary preparations. I should not advise, with my present acquired knowledge, the too long or too frequent use of coca in the treatment of neurotic heart. It is more particularly as a temporary help, when help, however, is most needed and sought for, that it should be used. Under these circumstances neither alcohol, ammonia, strychnin, nitroglycerin, digitalis, nor any other drug will be so soon and so distinctly valuable as coca. Even in those instances where pain, dyspnœa, palpitation; small, frequent, irregular pulse, and weak heart follow closely upon the general phenomena of acute infectious disease, such as pneumonia, typhoid fever, and la grippe notably, the best preparations of coca are simply invaluable. In some instances frequently repeated doses of tincture of strophanthus are temporarily even more rapidly and evidently beneficial than coca.

Especially is this true in young girls suffering from primary, essential anemia (chlorosis). In these cases I am convinced the heart muscle itself is also at fault, and requires rapid active stimulation, and in this respect strophanthus is to my mind a most useful remedy. I doubt if its value is enduring, and whenever I desire a prolonged, continuous action in giving tone and strength to cardiac muscular fibres, I invariably appeal to small, repeated doses of digitalis in some form, preferably the tablet triturates of the tincture, as they rarely occasion stomachal intolerance when properly made.

Finally, I would add that judicious use of a few antiseptic drugs, notably wood charcoal (Bellocque's), salts of bismuth, creosote, and the mineral acids, is extremely valuable whenever faulty metabolism proceeding from the stomach or intestines is clearly made out.

The following prescription borrowed from Gibson[1] is doubtless very useful at times for the flatulence of organic or functional angina :

℞—Sp. ammonii aromat.		♏ xv.
Sp. ætheris comp.,		
Sp. chloroformi	āā	♏ x.
Sodii bicarb.		gr. x.
Aq. menth. pip.		ʒ j.

Among the causes of acute symptoms connected with the presence of a cardiac neurosis I know of nothing to be avoided more than the immediate bad effects of a cold, high wind, or of wet and chilling of the extremities, especially the feet. The reflex inhibition of the heart in these instances evidently proceeds from the bulbar vasomotor centre, and passes down the vagal trunk to the heart, and notably to the coronary arteries. We can thus appreciate how it is that in true angina pectoris such effect from this or other analogous cause has been immediately or rapidly fatal. From a few facts recently observed it would appear that we may occasionally obtain the happiest relief of most threatening symptoms from the internal use of solution of adrenalin. Even in senile cases, in which the other cardiac stimulants had been used without apparent

[1] Practice of Medicine, vol. ii. p. 160.

Note.—The Morison Lectures on "The Nervous Affections of the Heart," by G. A. Gibson, in Edinburgh Medical Journal, 1902, vol. xii., and 1903, vol. xiii., are deserving of very high praise.

good results, and where no doubt pronounced organic changes of the heart existed, great temporary good effects upon the cardiac force and rhythm were obtained after one or more doses of this drug.

I believe in this connection we may profitably learn much from Dr. T. C. Janeway's observations in neuropathic individuals, and thus base our clinical views on one of the latest improved instruments of applied science—*i. e.*, the sphygmomanometer. Janeway writes: "I have seen markedly neurasthenic persons with rather low normal systolic pressure and diminished blood pressure. I am inclined to doubt the constancy of high tension in the neurotic." Thus we clearly see why adrenalin may be rationally of the greatest use at times. But Janeway wisely adds: "One must be especially careful not to confuse the neurasthenia, which is sometimes due to vascular or kidney disease, with its essential hypertension and the reported high normal readings in simple neurasthenics."[1]

I have found that some German observers, notably Krehl, His, Romberg, Leyden, and Martins, have made observations quite similar to those I have tried, though imperfectly, to record. It is claimed, indeed, not only that cardiac dilatation is sometimes of purely nervous origin, but also that some degree of cardiac hypertrophy may be of this provenance. It is also averred, and of this I am more and more convinced, that certain soft, blowing murmurs, which have been hitherto usually regarded as of hemic origin, are due essentially to imperfect or irregular muscular control in the heart muscle, whether it be of walls or valves, and this again is of nervous origin.

As to those instances in which there is for many a day reasonable doubt as to the existence of a myocarditis as being explanatory of palpitations, rapidity or slowness of heart action, irregularity, intermittences, lessened force, localized pain, cardiac asthma, etc., rather than neurosal disturbances, nothing better has been said up to the present time, so far as I know, than by Dr. Herman H. Hoppe. So late as 1902 he writes as follows: "Before the diagnosis of dilatation or hypertrophy can be made in neurosis of the heart, we must

[1] The Clinical Study of Blood Pressure, p. 257. Appleton & Co., 1904.

carefully exclude all organic lesions, and must likewise bear in mind that we may have at the same time both an organic lesion and a neurosis. It is well to remember, however, that we may have as a result of simple neurosis of the heart undoubted dilatation and perhaps hypertrophy."[1]

In practice these cases are sometimes most difficult to differentiate, and careful, prolonged enquiry and observation will alone enable us to reach an accurate and satisfactory conclusion. Of course, if the patient is young and without a history of previous acute rheumatic or other prolonged febrile attacks, we may often be almost assured that no organic changes exist either in the myocardium, or ganglia, or nerves of the heart. On the other hand, if the patient be of middle life we become properly and naturally suspicious about myocarditis and sclerosis of the coronary arteries. In those instances where there has been a former severe attack of influenza, we have, as we know, a causative factor of considerable importance in producing organic nervous and muscular changes in the heart. We may then have both combined in this organ, and it becomes well-nigh impossible for weeks and months to determine what symptoms belong to the loss of nervous control and what to deficient muscular power. The correct differential diagnosis between neurasthenia of the heart and the cases of organic change becomes all important from the point of view of treatment.

In the former examples there can be little doubt that life in the open air with increasing passive or active exercises (massage, resistant movements, graded hill climbing, etc.) is most useful and necessary. In patients affected with cardiac organic changes, especially if at all pronounced, the problem as to whether or no to advise exercise is fraught with risk or peril, with respect of improvement or cure. More than once I have been impressed with the importance and value of this point of view when I have considered the judiciousness of the present fashionable Nauheim treatment. There is no doubt in my mind that I have seen several examples of considerable and quite lasting improvement in signs and symptoms from a "cure" at this spa. On the other hand, I am now inclined to the

[1] Journal of the American Medical Association, May 24, 1904, p. 1346.

belief that these were cases in whch the neurosal element was predominant, although not fully recognized, and we could thus rationally account for the decided benefits obtained. In view of my own study and observations, I continue to oppose the sending of manifest cases of organic heart changes to Nauheim with the hope of remedial good effects. In general, I should expect positive harm to result, and the more energetic and prolonged the treatment, the greater the harm. Are not many cases reported by Bezly Thorne, Satterthwaite, and other warm advocates of Nauheim treatment, abroad or at home, merely cases of cardiac dilatation, and perhaps hypertrophy, largely due to functional disability of cardiac ganglia and nerves? Of course, as we now know, and as I have previously stated, automatic, rhythmic power exists essentially in cardiac muscular fibres, and yet it is clear arrhythmia, intermittences, palpitation, nervous angina, tachycardia, etc., may be largely influenced or caused by innumerable psychic and physical agencies, and even though the cardiac ganglia and nerves are purely sensory. Similarly, I am equally confident at present that cardiac bruits more or less intense and prolonged, usually however soft in character, may be wholly of nervous origin, and quite independent of recognizable blood changes, or changes in the locality and size of the heart. According to Whitaker,[1] while the cardiac ganglia are "denied the office of presiding over the motion of the heart, they have the higher one of perceiving the first influence of failing nutrition or toxic impression." It is readily understood that in diminished nutrition we may find the explanation of many cardiac neuroses, and also of altered activity on the part of the cardiac ganglia. (Hoppe.)

In all cardiac affections we should bear in mind constantly how difficult it is during life to determine accurately slight deviations from the normal, whether it be of valves, vessels, muscles, or nerves. On the autopsy table how often do these difficulties clear up and appear almost transparent, so simple are they and so easy at times of recognition! No doubt many cases I have seen might be classed as neurasthenia of the heart. In others this condition was not

[1] American Practice of Medicine, vol. iv. Quoted by Hoppe.

clearly defined, in view of certain symptoms present, and exception could be taken to it. Since reading Dr. William H. Thomson's able and exhaustive treatise on *Graves' Disease*,[1] and particularly what relates to cases without goitre, I have the impression that I have more than once treated a patient with persistent tachycardia and pronounced digestive disturbances, and did not recognize the nature of the case because neither exophthalmos nor enlargement of the thyroid was present. It is true that I have felt the importance for many years of rigid dietary and the use of suitable drugs to diminish or correct the effects of autointoxication from the gastro-intestinal tract, in expressions of the neurotic heart. On the other hand, I am now convinced that the periodic use of a mercurial, and the employment of phosphate, sulphate, and salicylate of soda, with a tumblerful of hot water each morning, as well as insistence upon a dietary largely of fermented milk, as matzoon or koumyss, is very important, not to say essential, at times. To no one is the profession more indebted than to Dr. Thomson for numerous and convincing facts with which he has supported this view.

Dr. David Drummond has made a careful study of cardiac functional murmurs in articles of the London *Lancet*[2] and the *British Medical Journal*.[3] In one class he puts those of cardiomuscular origin. The murmurs may be, he writes, systolic, postsystolic, or even diastolic. "Some are loudest when patient is standing, and disappear when he is at rest in the recumbent posture, while the reverse is the case with others." In a few of the cases the possibility of slight hypertrophy existed. It is difficult, however, to determine the size of the heart in cases of nervous palpitation. A *temporary* increase of impulse and outward displacement of the apex beat "cannot be regarded as a sufficient indication of hypertrophy or dilatation." In regard to the cardiac dilatation which is occasionally clearly defined in the prolonged and uninterrupted tachycardia of Graves' disease, *that* I regard as a very different and distinct condition from the one I have in part studied in the foregoing paper.

In concluding this paper, I wish to say that I could have largely increased the number and variety of my cases. I have not done so

[1] New York, 1904. Wm. Wood & Co.
[2] July 27, 1895, and April 10, 1897.
[3] November 1, 1902.

for fear lest I weary my readers or hearers, and thus take from, rather than add to, the interest of my clinical report of personal observation and belief. I would specially emphasize certain facts which seem to me true, but as yet either insufficiently recorded or recognized, viz.:

1. An apparent or evident slight cardiac enlargement with or without dilatation, and it may be slight hypertrophy, occasioned by or proceeding directly from a cardiac neurosis.

2. A condition of secondary anemia, as shown by careful microscopic blood examination, with count and differentiation of white corpuscles, which remain stationary for a long while, despite the use of chalybeates and most rational treatment from every standpoint.

3. The absolute or relative uselessness of digitalis, notably, unless the heart muscle is involved, and even in these instances, for acute manifestations of weakness or failure, strophanthus is far more useful.

4. Impaired nutrition, at a given period, of the muscular walls of the heart under the immediate dependence, probably, of diminished nervous energy, gives rise to slight cardiac dilatation at times which subsequently, under judicious treatment, remains stationary as to amount, and becomes functionally compensated.

CHRONIC POISONING BY ACETANILID.

By D. D. STEWART, M.D.,
OF PHILADELPHIA.

That chronic poisoning, characterized by degenerative changes in the blood and by physical disability, may result from the continued ingestion of anilin derivatives is well known, as it is also well recognized that acetanilid, one of these products, because of its small cost and its toxicity in excess of others of this group in common use, renders it particularly liable to be the offending agent. Acetanilid is the chief ingredient in headache powders so generally dispensed by pharmacists without prescription, as it is in certain secret nostrums both in use by the rank and file of the profession, and, unfortunately, thus introduced by them to the laity.

The toxicity of acetanilid, in common with related coal-tar products of the antipyretic group, has long been known, and the serious, if not fatal, results which may follow its incautious use in fevers and debilitating conditions should have in past years been brought forcibly to the attention of the reckless seeker after a remedy to reduce temperature or to assuage pain. But the knowledge of the toxic action of this group, and especially of acetanilid, has had little effect on the unscrupulous, who have found a ready market for compounds offered as analgesics. Attempts have been made to overcome the immediate ill effects of the drug by combining it with small quantities of caffein, and a very popular nostrum now—I should suppose pretty well known throughout the civilized world—contains these as chief ingredients, which also enter into the makeup of presumably nearly all headache powders.

I have under observation a man, aged forty years, of splendid physical development, who recently consulted me concerning his

digestion. Although of good habits, not given to alcohol and but moderately to tobacco, getting an abundance of fresh air and exercise, and having no element in his life unconducive to well-being, he has been, unaccountably, more or less out of sorts for the past year or two. There were loss of cardiac tone, a sallow, peculiar, dusky hue of the skin, and anorexia. Examination of the stomach contents showed hyperchlorhydria, a condition not regarded as responsible for his partial invalidism. My laboratory associate, Dr. Ghriskey, like myself, was struck by the dusky hue of the skin, not to be attributed to respiratory or cardiac disability. Enquiry elicited the fact that for two or three years his habit had been to take headache powders. He had formed the habit of resorting to them at first for the relief of headache, and finally when at all out of sorts. He invariably had taken one on rising in the morning, and sometimes several (eight to ten) through the day, but often only two or three. These were a proprietary preparation sold under the name of "headache powders,"[1] or a frank prescription, which he obtained without a writing, of acetanilid and caffein, or antikamnia, which he also had combined with acetanilid and salol. Lately he had taken very few; that morning three before his visit to me. The blood, as it stood on the ear, showed the characteristic chocolate hue, indicating the presence of methemoglobin. Hemoglobin estimation was thus impossible. Inspection showed moderate variation in size and shape of erythrocytes. These were 3,860,000 per c.mm.; the leukocytes, 9200. Differential count of 550 leukocytes (Dr. Ghriskey): polymorphonuclears, 62.20 per cent.; small lymphocytes, 13.66 per cent.; large lymphocytes, 23.81 per cent.; eosinophiles, 0.33 per cent.

Decided variation in size of lymphocytes, from very small to large. The greater number were of medium size. Of the large, 18 were in the transitional form. During the above enumeration there were noted 1 megaloblast and 1 normoblast. Blood plaques were increased.

The blood examination was made five hours after the only meal of the day, a breakfast of the whites of two eggs, toast, and two

[1] One of these, a proprietary preparation largely advertised and sold in Philadelphia under the name of a certain doctor's headache powder, I found by analysis to consist solely of acetanilid, with a little coloring matter.

cups of weak tea. There was, therefore, present a pathologic leukocytosis and a diminution in the erythrocytes, the cause of which, an acetanilid toxemia, was not hard to seek, other factors being excluded by careful enquiry. The urine showed nothing characteristic.

This case of mild acetanilid poisoning is mentioned in passing as an example of one of perhaps many similar in which a slight or greater degree of invalidism might be traced to the incautious formation of the acetanilid, phenacetin, or a similar habit.

I recall the case of a woman, aged about thirty-eight years, under observation some years ago, who had curious attacks of cardiac debility, attended with dyspnea, and on one occasion marked edema of the legs. A grave form of mitral disease had been diagnosed by her previous attendant, a therapeutist of eminence. I saw her often, casually, in attendance on a member of her family. In several examinations there was absolutely no indication of cardiac disease, valvular or otherwise, and no history of any ailment that could have been a factor in originating such. The patient was of more than ordinary robust build; the hue of the skin was habitually dusky and the breath intensely, peculiarly fetid. I discovered that for a long time she had been a phenacetin habitué. Alcohol, which she had lately become addicted to through it having been prescribed for the cardiac condition, I regarded as a factor in contributing to the *fœtor ex ore*.

While one can understand the tendency to enslavement possessed over its unfortunate victim by alcohol, by morphin, by cocain, and the like, it is difficult to comprehend the employment of these coal-tar analgesics to the extent that a distinct addiction to their use is established, and yet that such is the case there is no doubt, even when their use is acquired other than for the relief of pain.

Luce[1] reported two interesting instances of acetanilid addiction, in which the drug had been originally prescribed for pelvic pain.

The first of these, when seen by Dr. Luce, was hysteric and emaciated. There were recurring revulsions, edema of the inferior extremities, feeble and irregular heart, blueness of the mucous membranes, but pallor of the skin; albumin and casts in the

[1] American Medicine, September 26, 1903.

urine. The initial diagnosis was uremia. Later, among the patient's belongings a large quantity of acetanilid was discovered. When the drug was withheld the patient "soon began to exhibit all the traits peculiar to the confirmed morphinomaniac—moral depravity and the like." She employed every possible means to obtain the drug, attempting even to bribe the nurse, and, this failing, the members of the family. Recovery followed under careful treatment, and in six months the patient was perfectly well, and had remained so to some months later, at the time of the report.

The second case was very similar. So secret was the habit that the attendant, with whom Dr. Luce saw the case, would not entertain the notion of a hidden drug habit. The use of acetanilid was accidentally discovered, and its withdrawal attended with similar difficulties, as in the other case.

In the interesting case of Stengel and White,[1] under their care in the University Hospital, which, in character of blood changes, that of mine to be reported closely resembles, concealment of the habit was in evidence, and although the patient's ill-physical and blood condition early aroused a suspicion on the part of Dr. Stengel of some form of hemolytic poisoning, it was only with the greatest difficulty ascertained. The case is briefly as follows:

Miss R., aged twenty-five years, had suffered from insomnia for five years, resulting from neuralgia, and had been given chloral and other drugs for its amelioration. There had been much gastric disturbance; excessive cyanosis for five years; skin of a leaden hue; emaciation; feeble pulse; rapid, weak heart action; cardiac enlargement; systolic murmur heard over the whole precordia; venous hum and thrill in the neck; slight liver enlargement; spleen easily palpable; more or less edema of legs for several years; urine claret colored; specific gravity, 1024; albumin; no glucose; granular casts. Blood examination: erythrocytes, various counts, from 1,860,000 to 3,040,000; leukocytes, 19,800; no methemoglobin or hematoporphyrin discovered in blood or urine (Dr. Edsall).

Acetanilid addiction had been established through taking the drug for neuralgia. The habit was recent and unknown to

[1] University of Pennsylvania Med. Bull., February, 1903.

former attendants. One had regarded the case as valvular disease; another as mediastinal tumor; others had thought the cardiac condition could not account for the cyanosis; while a prominent clinician had diagnosed a tear in the interventricular septum. Through the patient being detected in receiving a package of acetanilid capsules, she finally admitted having been taking the drug in large quantities for some five years, and had continued its secret use in the hospital. On its withdrawal improvement was progressively manifest, save for a few days, when a capsule containing phenacetin was administered; then cyanosis, which had quite disappeared, returned. The signs of cardiac disability soon entirely disappeared and the patient was finally discharged "practically well in every respect."

I wish now to report a recently observed case of my own—of acetanilid addiction—in which the habit had been formed, not for the relief of pain, but through the drug having originally been prescribed for nervousness and insomnia. The point of special interest involved is the blood condition, the picture of which, if its chocolate hue, evident in the earlier examination, and the slight leukocytosis were disregarded, would appear that of pernicious anemia, characteristic of the blood condition observed by Stengel in his case (though in the case to be related present in less degree), and, as usual in the blood studies made by Ehrlich and Lindenthal, Krönig, and others, in certain cases of poisoning by anilin derivatives. The case is as follows:

A. F., male, aged fifty years, merchant, had been brought to Philadelphia from a distant part of the State to consult a kinsman, a physician, concerning his progressively increasing ill health, and was referred to me. He had begun to ail about two years before; became debilitated and lost weight. Segments of a tapeworm were discovered in July, and the entire worm was believed to have been voided in October. He continued, however, to decline in health. His stomach had been upset for a long time; anorexia was usual and frequent vomiting common, on which account lately he had eaten very little, and chiefly liquid food. He felt required to take a small amount of whisky daily, and a very small quantity affected him. His usual weight was 140 pounds, but he had now declined to 116. I was summoned to see him at his hotel on March 13, 1905. He was abed,

profoundly debilitated; was stuporous, and replied incoherently to questions. He had stood the journey to the city badly. The skin was of a dusky hue; the mucous membranes were pallid and anemic looking; heart feeble, but free from enlargement or adventitious sounds; outline of liver dulness slightly increased; spleen not palpable; right kidney loose and easily grasped; inferior border of stomach on the line with the umbilicus.

On the following day he was brought to my office for further examination. His appearance was that of a profoundly ill man. He was apathetic; there was marked mental hebetude, as was noticed the previous night, and so debilitated was he that he could scarcely speak. The heart sounds were much enfeebled and the pulse at the wrist barely perceptible. There had been a good deal of pain in the thighs and legs, with paresthetic sensations in the extremities. Edema was not present. The knee-jerks were absent, and only a slight flicker evident to reinforcement. The pupils reacted to light and accommodation; station impaired, but evidently due to debility, and not to loss of coordination; no tactile loss. Blood which exuded from puncture for examination was a deep chocolate color. Inspection showed poikilocytosis and variation in size of corpuscles. The urine was of unusually high color, resembling that of Madeira wine or porter, and had a peculiarly fetid, aromatic odor. Interrogation of his wife and himself elicited the information that for two or more years he had acquired the habit of taking antikamnia, which had been originally prescribed by his attendant for the relief of insomnia and nervousness; that for several years, at least two, he had taken daily some twelve tablets of either plain antikamnia or of antikamnia with codein, and this custom he maintained to the present, totally unaware of its effect in producing the present condition, which was regarded as the result of the gastric disorder. He had, besides, about a year ago, taken for a while two ounces of somnos at night. This he had not used for a long time. The antikamnia preparation was his mainstay, and the only drug now used. His physician, he said, had discovered glucose in the urine a year or so before, although the twenty-four-hour quantity never exceeded two pints. He himself had noticed the peculiar color and odor of the urine for a long time, and it was so evident when "diabetes" was diagnosed.

March 14th. Urine clear, though very dark-brown color; odor peculiarly aromatic and resembling somewhat that of burnt caramel; acid; sp. gr., 1026; albumin, marked reaction; glucose absent, though Fehling's test reduced; bile pigment absent (ether and iodin test). Microscopic examination (centrifuged specimen): few granular and hyaline casts; cylindroids; scattered red blood corpuscles and leukocytes. It was noted that a specimen should be examined for methemoglobin and hematoporphyrin.

Blood Examination, March 14th. Chocolate color. Hemoglobin estimation then impossible. Three days later the blood was of normal hue; then hemoglobin 60; erythrocytes, 2,522,524; leukocytes, 9700. Inspection shows variation in size and shape of erythrocytes. In less than half an hour's examination (Dr. Ghriskey) of a stained smear there were 7 normoblasts and 1 megaloblast seen.

Further blood report by Dr. Ghriskey: Variation in size and shape of erythrocytes; moderate polychromatophilia; stray erythrocytes, showing granular degeneration; blood plaques notably present; nucleated red corpuscles; normoblasts 407 per c.mm.; megaloblasts, 58.2 per c.mm. Differential count of 500 leukocytes: polymorphonuclear, 65 per cent.; small lymphocytes, 25.6 per cent.; large lymphocytes, 9.8 per cent.; eosinophiles, 0.06 per cent. During the above count there were observed 21 normoblasts and 3 megaloblasts. The nuclei of these cells were generally round in shape. Only several showed a tendency to segmentation.

March 15th. Examination of stomach contents. Fasting, took meal of bread and tea at 9.30 A.M.; at 11 A.M. lavage showed but little remaining; at 11.45 A.M. 60 gm. stale bread; 250 c.c. weak tea; 30 c.c. removed at 12.55 P.M. The color and odor of removed contents somewhat that of urine. Total acidity, 23; HCl absent to Günzberg.

The antikamnia and the small quantity of whisky he had been taking were ordered absolutely discontinued, and he was placed in the care of a competent nurse. Daily morning lavage was ordered, and menthol valerianate was prescribed for the control of nausea and vomiting. He was fed every three hours by day and given an abundance of pure water.

On March 17th the blood which exuded from the puncture for examination was normal in color.

Examination of stomach contents, March 17th. At 9 A.M. ate one roll, one soft-boiled egg, cup of tea. At 11.20 A.M. 40 c.c. were easily removed. Fairly normal appearing contents, well but unevenly solved; considerable ropy mucus; filtrate, light amber; total acidity, 64; Gunzberg, strong; Toepfer, 45; good digestion, with normal HCl, was therefore present.

Urine, March 17th: 550 c.c. in twenty-four hours; color and odor as previously described; acid; sp. gr., 1022; bile absent; albumin, well-marked reaction. Microscopic examination: hyaline casts; cylindroids; scattered red blood corpuscles and leukocytes. Specimen sent to a chemist for examination as to presence of abnormal constituents, the result of blood disintegration. Under a few days' rest abed—careful feeding, daily lavage, a bitter, acid mixture before meals, iron albuminate, strychnin, and digitalin—there was a rapid improvement, and on March 25th, eleven days after he came under observation, there was a marked change for the better, and he insisted on returning to his home to direct his business. The heart sounds were now fairly strong, the dusky hue of the skin had much lessened, and the pains in the legs and thighs had disappeared. The knee-jerks were slightly evident without reinforcement. He was much stronger. Nausea and vomiting had disappeared. He had a good appetite, and for several days had been able to eat three full meals, with light food between. The urine had become normal in amount and the peculiar odor had disappeared. March 23d it was 1450 c.c. in twenty-four hours. The characteristic odor was slightly present in this mixed specimen, but not in a single specimen voided two days before.

April 12th, eighteen days after his return, in response to an enquiry as to his condition, he replied that he steadily continued to improve; weighed 124 pounds, ate well, was "gaining strength daily," although he slept badly and was nervous at night, and that the hue of the skin was more natural. He was still taking the tonics prescribed, including arsenic, and had not resumed the antikamnia.

It is regretted that the record in this case is not complete in that a spectroscopic examination of the blood was not made, as was contemplated, and that no report is at hand as to the presence of methemoglobin and hematoporphyrin in the urine and

the character of the body causing the peculiar odor. These examinations were noted to be made, but the case was seen in the midst of active private practice, and the blood clearing so quickly left no time then to arrange for a spectroscopic examination. The chemist to whom the urine was sent for this examination neglected to undertake it. That methemoglobin was present in the blood, the appearance of the latter at the first examination strongly suggests, and that bodies characteristic of blood disintegration existed in the urine is quite likely. This non-isolation is regrettable.

In these cases of severe chronic poisoning by acetanilid [1] and related coal-tar products the symptoms are usually very similar as concerns progressive mental and physical debility, which later often reaches a high grade. There are cardiac weaknesses, more or less pronounced cyanosis, and characteristic changes in the blood, indicative of the pernicious action of a hemolytic agent. Apart from the usual chocolate hue of the blood so noticeable on puncture, the blood picture, were it not for an almost invariably present leukocytosis, would suggest pernicious anemia. There is a diminution in the erythrocytes, with variation in their size and shape, the presence of erythroblasts often in larger numbers than is encountered in pernicious anemia, polychromatophilic cells, and of cells the protoplasm of which is undergoing granular degeneration. The blood plaques are usually notably increased. A leukocytosis is common, the increase being, it is reported, usually in the polymorphonuclear elements. There were, however, in my two cases, which were uncomplicated, 37 and 35 per cent., respectively, of lymphocytes. In several cases reported the leukocyte increase may have been influenced by a coincident ailment adding its quota, and this also influencing the relative polymorphonuclear increase. Thus in Stengel's case there was an alveolar abscess, and in that of Hall[2] bleeding hemorrhoids and rectal fistule, and in Cabot's case nasal carcinoma. Curiously, in Cabot's case,[3] in which the blood as it stood on the ear presented the character-

[1] It should be here remarked that the composition of antikamnia, the compound of acetanilid used in this case and that employed in many others in which "headache powder" is the form ingested, is, as is well known, a mixture of acetanilid, citrated caffein, and sodium bicarbonate. Various analyses of antikamnia show it to contain approximately 70 per cent. of acetanilid.

[2] Boston Med. and Surg. Journal, December, 1903.

[3] Philadelphia Medical Journal, November 29, 1902.

istic chocolate hue, and in which, therefore, the hemoglobin was not estimable, there was a polycythemia. The count ran over 6,000,000 on one occasion, and the only noticeable abnormalities in the stained specimen were slight poikilocytosis, granular stippling of many of the red cells, and undue fragility of the leukocytes. Erythroblasts were not in evidence. Methemoglobin was easily demonstrable in both blood and urine. The patient's general condition was good, despite the evident cyanosis. Such a case might superficially suggest the condition which lately has attracted considerable attention—chronic cyanosis with polycythemia and enlargement of the spleen. Hall, in reporting his case of acetanilid poisoning, called attention to the likelihood of the initial confusion, and laid stress on the presence of characteristic anemia, etc.

INTRAPLEURAL LIPOMA; ACUTE PERICARDITIS; PERICARDIAL EXPLORATION.

By R. H. FITZ, M.D.,
OF BOSTON.

It is well known that in certain individuals, especially the obese, a large quantity of fat tissue may be found beneath the pleura, and it is easily conceived that a lipoma might be developed from this subpleural fat. Cruveilhier,[1] indeed, mentions the occurrence of fatty tumors of the diaphragm which have forced their way through the fibres of this muscle from the subperitoneal fat, at times accumulated behind the ensiform cartilage. The attached peritoneum is stated to form a true hernial pouch, ready to receive the abdominal viscera.

A rounded, lobulated, subpleural lipoma, somewhat larger than a plover's egg, was found by Clark[2] in the right pleural cavity of a woman sixty-five years of age. Its "base was spread out between the muscle fibres of the diaphragm like the mycelium of a mushroom," and the tumor resembled "at first sight a diaphragmatic omental hernia." He calls attention to a normal "outgrowth of fat from the diaphragm, situated on the right side anteriorly close to the reflection of the pericardial pleura on to the diaphragm. This may, in cases of general obesity, become occasionally so increased in amount as almost to assume the appearance of a fatty tumor, but does not, of course, constitute a true tumor, since it is but part of a general physiologic process."

Conner[3] records a somewhat similar observation. He found in an elderly woman who died of cerebral hemorrhage a sessile, fatty tumor, measuring 4 x 3 cm. It was covered by pleura and

[1] Traité d'anat. path. gén., 1856, iii. 310.
[2] Trans. Path. Soc., London, 1887, xxxviii. 324.
[3] Proc. N. Y. Path. Soc., 1897–98, 43.

projected from the diaphragm into the left pleural cavity a little to the left of the apex of the heart. At its base there appeared to be a deficiency in the diaphragm, which was offered as a possible explanation of the origin of the tumor.

The subpleural fat along the intercostal spaces is often abundant, and Rokitansky[1] states that, at times, it projects into the pleural cavity as notable, lobulated masses.

Lancereaux[2] knows of but one well-authenticated instance of a subpleural lipoma.

Chiari[3] is stated to have observed in an elderly female a pendulous lipoma of the size of a walnut projecting into the pleural cavity from the seventh left rib.

The subpleural lipoma of the costal wall may become so large as to be of practical importance, as illustrated by the experience of Czerny.[4] This surgeon removed a lipoma of the size and shape of a man's head from below the left shoulder-blade of a male patient eighteen years old. The tumor was of rapid growth, and was found at the operation to be continued into the thorax between the seventh and eighth ribs, which were separated by a gap of the size of a hen's egg. The patient died of septic pleurisy, and the subpleural cavity within the chest, from which the innermost portion of the tumor was removed, contained several sinuses. The growth was considered to have proceeded from the endothoracic fascia beneath the pleura. Several years later a like experience was published by Plettner[5] as having been met by Volkmann in the practice of another surgeon. An elderly woman had a lipoma of the size of a child's head projecting from the left wall of the thorax. At the operation it was found to be prolonged into the chest by a pedicle between the fourth and fifth ribs in the axillary line. The outer portion of the tumor was removed, but the patient died of septic pleurisy and pericarditis, due to an ichorous inflammation of the pedicle. At the autopsy the latter was found to be continued into a flattened, subpleural lipoma as large as a hen's egg.

Gussenbauer[6] examined a female patient, twenty-nine years

[1] Lehrb. d. Path. Anat., 1861, iii., 39.
[2] Traité d'anat. path., 1879–1881, ii., 147.
[3] Gussenbauer, Arch. f. klin. Chir., 1892, xliii., Festschr., 323.
[4] Wien. med. Woch., 1875, xxv., 166.
[5] Inaug. Diss., Halle, 1889.
[6] Loc. cit., 322.

old, who had a tumor at the upper border of the left mammary gland. It was of the size of a nut, and lay in the second intercostal space between the edge of the sternum and mammillary line, beneath the mammary gland and the pectoral muscles. The latter structures could be moved over the tumor, which could not be displaced from the thoracic wall. Three years later the patient again was seen, the tumor having become enlarged in the mean time, and especially within the previous months. It was regarded as an encapsulated lipoma proceeding from the second intercostal space, on account of its mobility, consistency, lobulated surface, and place of fixation. Its matrix was considered to be the subpleural fat tissue, as in the case reported by Czerny, which Gussenbauer also had seen, and in accordance with the previously mentioned statement of Rokitansky concerning the subpleural fat. At the operation a pedicle twice as thick as the finger was extended from the tumor into the chest through the widened second intercostal space. Traction upon the pedicle brought to view a portion of the intrathoracic tumor. The latter was enucleated by the finger from its subpleural attachments and was removed. It was a little smaller than the outer tumor, about the size of a man's fist, and was contained within a subpleural cavity. The entire tumor was twice as large as the fist and weighed over five hundred grams. The patient recovered.

The fat tissue of the mediastinum also is known to have served as the place of origin of intrathoracic lipomata, which have projected externally from the wall of the chest, and have been submitted to surgical treatment. Cruveilhier[1] states that during an operation for the removal of a lipoma in front of the sternum the surgeon found several prolongations continued from it along the edges of this bone into the anterior mediastinum. Most of these were withdrawn and cut off. The patient died of suppuration of the anterior mediastinum. He mentions[2] also that Morel-Lavallée successfully removed from the sternal region the superficial portion of a lipoma, which was continued into the anterior mediastinum by a prolongation, which was not disturbed.

Krönlein[3] reports the case of a female infant, one year old, operated upon by Langenbeck. At the age of six months a small

[1] Op. cit., 315.
[2] Op. cit., 322.
[3] Arch. f. klin. Chir., 1877, xxi., Supplement 157.

tumor near the right breast was noticed by the parents. It grew rapidly, and at the time of operation formed a lobulated mass, extending from the right axillary line to 3 cm. beyond the left sternal edge and from two finger breadths below the right clavicle to the xiphoid cartilage. At the left of the tumor there was dulness on percussion, preventing an accurate determination of the outlines of the heart. The apex beat was palpable in the sixth interspace, 2 cm. outside the mammillary line. The tumor increased considerably in size in the course of five days, and Langenbeck suggested its probable lipomatous character and congenital origin from the anterior mediastinum, with subsequent perforation of the thoracic wall. On exposure of the tumor it was found to be continued into the chest through the third intercostal space 1 cm. from the right sternal edge by a pedicle as thick as the thumb. The pedicle was cut across at the level of the ribs and the external tumor removed. The infant died of erysipelas. At the autopsy a rounded lipoma, as large as a child's head and covered with a firm, fibrous capsule, was found completely filling the anterior mediastinum and continuous with the pedicle above mentioned. It projected 2 to 3 cm. beyond the right sternal edge and filled almost the entire anterolateral portion of the left thoracic cavity, leaving only a small space below and behind, in which lay the compressed lung and the displaced heart.

The following unique case shows that subpleural lipomata may have a medical as well as a surgical interest: The patient, a fisherman, aged thirty-four years, lean, always well, with the exception of a "typhopneumonia," entered the Massachusetts General Hospital January 4, 1905. He had been seized with a severe chill ten days previously, followed by pain across the chest aggravated on deep inspiration. There was a distressing cough, with rusty sputum, and considerable dyspnea. The physical signs indicated consolidation of the left upper lobe.

In the left axilla, corresponding to the region of the inferior third of the lower lobe of the lung, there were dulness on percussion and absence of respiratory and vocal sounds. The midaxillary region was occupied by a wedge of normal resonance and respiratory sounds, with its apex in the vicinity of the left nipple. There were dulness, diminished fremitus, and feeble vocal and respiratory sounds in the left back between the angle of the scapula and the spine. Numerous medium, moist rales were heard at the base of the left lung behind. The left border of cardiac dulness was four and three-fourths inches from the median line, and the right border dulness was at the right sternal edge. The apex beat was audible in the fifth intercostal space, four and one-

half inches to the left of the median line. The heart sounds were regular, rapid, and distant; the second sound was strong at the apex. Adventitious sounds were not heard. There were 41,200 leukocytes per cubic millimeter and 80 per cent. of hemoglobin.

During the subsequent four days the temperature fell from 104° to 101°, near which latter point it persisted. In the same period of time the pulse fell from 145 to 100, near which rate it subsequently remained. The respiration at first was 50 to 35, but after five days ranged from 25 to 30, till within two days of his death, when it rapidly rose to 45. Death occurred two weeks after entering the hospital.

For a few days he was mildly delirious, the white count remained high, the signs of consolidation persisted, but on the fifth day the failure to improve and and the faintness of the heart sounds suggested the possibility of an acute pericarditis.

The general condition of the patient then became somewhat better, but the physical signs persisted, and the leukocyte count remained high. Attention was constantly directed to the pericardium, as well as to the lungs and pleuræ, in search of an explanation of the persistent elevation of temperature and the continued leukocytosis.

Ten days after entrance and the twentieth day of the disease, it was noted that the signs of consolidation continued in the left lung. The right border of cardiac dulness remained at the right sternal edge, the cardiohepatic angle was obliterated, and the heart sounds were faintly heard. The pulse became paradoxic. Although dulness persisted in the left back between the angle of the scapula and the spinal column, the vocal resonance and fremitus and the respiratory sounds were normal.

On the following day, the twenty-first of the disease, the pericardium was tapped in the fifth interspace near the left border of the sternum, and again in the left fourth interspace some two inches from the sternal edge. Although the cannula entered at least an inch and a half in each place, and the surface of the heart was reached, there was no escape of fluid. Two days later, in consequence of attacks of dyspnea and cyanosis, although there was no change in the physical examination of the chest, the exploratory trocar and cannula were inserted through the sixth left interspace in the axillary line into the subjacent area of dulness, with the thought that pus might be present. The instrument entered readily between two and three inches and the tip was moved about freely. After withdrawal of the trocar no fluid escaped, nor did air enter the cannula. The trocar was reinserted and withdrawn, and a second attempt at aspiration was made, but without effect. When the cannula was removed, it was found to contain a fragment of soft material suggesting fibrin, but which on microscopic examination proved to be fat tissue.

My assistant, Dr. Beals, was asked to explore the pericardial cavity from the left xiphicostal angle after the patient's death, which took place the same day. He withdrew about a pint of creamy pus.

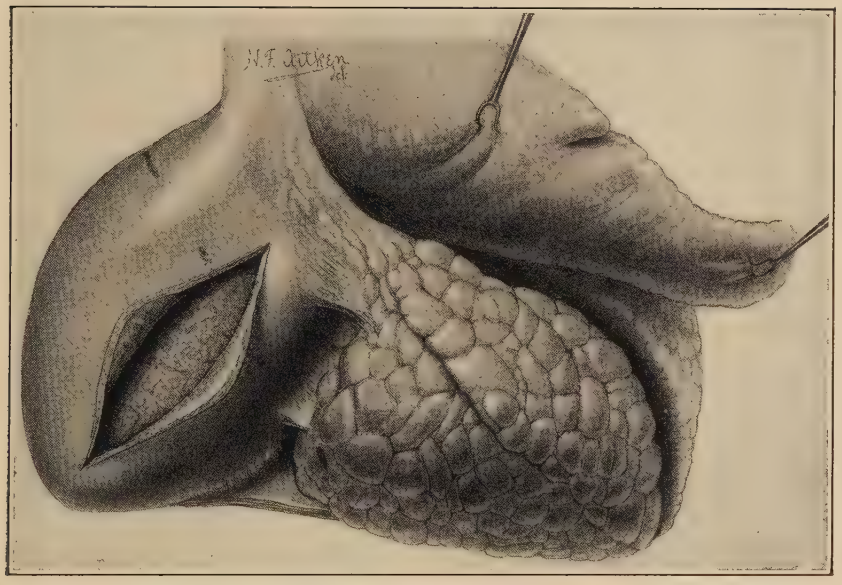
A postmortem examination was made by Dr. James H. Wright, from whose record the following abstracts are made: "On opening the pericardium a large

amount, probably 500 c.c., of yellowish opaque fluid gushes forth. . . . Adherent to the inner aspect of the pericardial sac and to the surface of the heart everywhere is a dirty yellowish, finely shaggy, or rough fibrinous layer, 1 to 3 mm. thick. . . . The epicardial fat over the right ventricle near the pulmonary artery is much larger in amount than normal, forming a layer 3 or 4 mm. thick. . . .

"Attached to the pericardium on the left side and apparently continuous with the fat tissue of the superior mediastinum is a large mass of fat tissue of about the volume of a newborn child's head, divided by delicate connective-tissue septa into larger and smaller lobules. It evidently occupied the inferior and anterior portions of the left pleural cavity, the left lung being behind and above it. The inferior lobe is of about one-third the normal volume. . . . On section it is dark red in color, moist, and not obviously atelectatic. The appearance of this lobe suggests rather a hypoplasia than atrophy and atelectasis. The large amount of fat tissue just referred to is more or less adherent by fibrous adhesions to the diaphragm, to the pericardium, to the parietal pleura, and to the inferior lobe of the left lung. Portions of it were left in the body on removal of the thoracic viscera. As far as could be determined the shape of the mass of fat tissue was more or less that of a pear, the small extremity being attached most firmly to the external surface of the pericardial sac along a line extending from the anterior mediastinum in the region of the pulmonary artery (where it seemed to be continuous with the fat tissue of the pericardium) downward on the left side toward the posterior mediastinum. The mass of fat tissue appeared to be covered in places by a thin, shiny layer resembling the pleura.

"The superior lobe of the left lung is voluminous and extremely resistant to the touch. On section the cut surface is grayish, granular, firm, and when scraped with a knife yields a rather thin, reddish fluid. The pleural surface of the superior lobe is grayish and opaque, not shiny. . . . Fluid of pericardium aspirated postmortem shows growth of pneumococci by culture. . . . Most of the air cells in the section from the superior lobe of the left lung contain an exudate consisting chiefly of fibrin in dense strands and masses. In a few places there is an outgrowth of fibrous tissue into the air cells, not sufficiently extensive to justify calling the condition organizing pneumonia. The appearances in the section indicate a lobar pneumonia in which resolution has not been thoroughly established."

It is evident from the history of the patient and from Dr. Wright's examination that a pneumococcal pericarditis developed without characteristic symptoms or signs in the course of an acute pneumonia of the left upper lobe, and that the resolution of the latter was delayed. Owing to the persistent solidification of this lobe and the pressure of a large intrapleural lipoma of mediastinal origin, the pericardial exudation was not enabled to cause a lateral increase of pericardial dulness; on the contrary,



Intrapleural lipoma proceeding from the fat tissue of the superior mediastinum.

it was made evident by aspiration that the fluid was accumulated behind and below the heart.

The congenital origin of the lipoma is indicated by the accompanying hypoplasia of the lower lobe of the left lung. Its discovery was wholly unexpected, although the physical signs and the result of aspiration would permit a diagnosis in a second case. Its significance to the physician lies in its presence being a satisfactory explanation for an unusual distribution of pericardial exudation, and its localization offers an opportunity of error in the diagnosis of a circumscribed pleuritic exudation.

It is a matter of common knowledge that even considerable quantities of liquid pericardial exudation occasionally escape recognition. Characteristic symptoms may lack and the heart adapt itself to the encumbrance of moderate accumulations of fluid, and, as a rule, the quantity present is small. Pericardial paracentesis, therefore, is of relatively infrequent occurrence. During a period of thirty-four years at the Massachusetts General Hospital there are noted in the index of the records 150 cases of acute pericarditis, of which 14 were tapped; 5 of these died, 4 were discharged much relieved, 2 relieved, and 3 well. In 4 cases no fluid was obtained, while in the remaining 8 quantities varying from one drachm to one quart were removed. In 6 cases less than four ounces were obtained.

Since October, 1896, evidence of acute pericarditis has been noted in twelve autopsies. The largest quantity of fluid found was nearly one pint, and in the patient concerned the existence of a pericarditis was not suggested until the day of death. In a second instance a half-pint was present, but in the majority of the cases the quantity of fluid observed was less than five ounces.

The diagnosis of an exudative pericarditis is determined by rational signs, indicative of an infectious process, and by physical signs, calling attention to the seat and extent of the exudation. The rational signs alone are not to be depended upon to direct suspicion to the pericardium, since pericarditis usually is secondary to an inflammatory process elsewhere—for example, in the lung, pleura, or peritoneum—the symptoms of which are likely to mask those proceeding from the pericardium. Especially significant in the etiology of the cases tapped in the hospital were acute pneumonia and rheumatism, each in four cases, while the peri-

carditis was regarded as primary in three instances. The diagnosis is comparatively easy when the course of the disease can be traced from the initial pain and friction sound to the gradually increasing area of cardiac dulness of characteristic outline, with fading rub and increasing remoteness of cardiac sounds. It is rendered more difficult when the adherent lungs prevent the lateral distention of the pericardial sac; the adjacent lung is solidified, the pleural cavity contains an exudation, or the anterior wall of the heart is united to the parietal pericardium by old or recent adhesions. To these familiar obstacles a new source of difficulty is to be added, viz., the intrapleural lipoma, especially when it attains the size and position shown in the case here reported, as well as in that of Krönlein-Langenbeck.

The experience above recorded indicates the essentially exploratory nature of pericardial paracentesis, and emphasizes the importance of a thorough exploration in doubtful cases. As usually performed, the needle is inserted into the fourth or fifth left intercostal space near the sternal edge, or some two inches from it. The failure to obtain fluid at these points in the case here reported led to the assumption that the exudation was largely fibrinous. The absence of an increased area of dulness at the right of the sternum negatived the thought of tapping at Rotch's point in the fifth right interspace one and one-half inches from the sternum. The positive result of the postmortem puncture in the left xiphicostal angle makes it obvious that this way into the pericardium should always be favored in cases of suspected exudation; if not in the first instance, certainly when aspiration at the other points has proven ineffectual.

Larrey[1] originally recommended this route for pericardial drainage, and gave specific directions for performing the operation. He was led so to do from having successfully drained in this region a stab wound, which gave satisfactory evidence of communicating with the pericardial cavity. Roberts,[2] however, objected to paracentesis in this situation, unless the case were exceptional, from the possibility of wounding the diaphragm and liver, and from the difficulty of determining the edge of the ensiform cartilage in fat persons. In two cases in which I have

[1] Clin. Chir., 1829, ii., 303.

[2] Paracentesis of Pericardium, 1880, 66.

punctured the pericardium in the left xiphicostal angle, although fluid was not obtained, no ill effect followed, and the condition of the patients improved, temporarily, at least, after the exploration was made.

From the facts above narrated, and from those reported by F. C. Shattuck[1] and others, an exploratory incision in the xiphicostal region seems advisable in urgent cases when exploratory puncture has afforded no relief.

Roberts[2] recommended exploratory incision as far as the pericardium when there was a doubt between a large pericardial exudation and a dilated heart. More recently he states[3] that incision is better than aspiration, even when the affection is not supposed to be purulent.

Brentano[4] advocates in all cases pericardial incision with previous costal resection as less dangerous than paracentesis, and Weintraud[5] prefers incision to paracentesis.

Although Roberts[6] now is in favor of exploratory aspiration in the upper part of the left xiphoid fossa, he considers that this region does not afford room for incision and drainage. Ogle and Allingham,[7] on the contrary, recommended the plan of reaching the pericardium originally outlined by Larrey, followed by the removal of two inches of the seventh left costal cartilage, if necessary.

Latham and Pendlebury[8] reported the successful performance of this operation with a vertical instead of an oblique incision, and the removal, also, of two inches of the sixth costal cartilage; and Pendlebury[9] has operated upon two additional cases, one of which recovered.

Mintz[10] also has successfully drained the pericardium in the region recommended by Larrey.

There is, therefore, no doubt that aspiration through the left xiphicostal space has disclosed pericardial exudation which was not made evident by puncture elsewhere, and that successful

1 Transactions of the Association of American Physicians, 1897, xii., 193–196.
2 Annals of Anat. and Surg., 1881, iv., 250.
3 Am. Jour. of the Med. Sci., 1897, cxiv., 649.
4 Deutsch. med. Woch., 1898, xxxii., 507.
5 Lehrb. der klin. Untersuch, Meth., 1905, ii., 380.
6 Am. Jour. of the Med. Sci., 1897, cxiv., 652.
7 Lancet, 1900, i., 693.
8 Ibid., 1903, i. 798.
9 Ibid., 1904, ii., 1145.
10 Zbl. f. Chir., 1904, xxxi., 59.

drainage has been established through the same region; consequently this route is to be recommended for exploratory aspiration, incision, and drainage, since it gives ample room (by resection of the costal cartilage, if necessary), is free from risk to the pleura and peritoneum, and enables injury of the internal mammary vessels to be avoided or controlled. In critical cases, when aspiration causes no outflow of fluid and the tip of the instrument can be moved about within the pericardium, exploratory incision should speedily follow.

DISCUSSION.

Dr. Ewing: In connection with Dr. Fitz's case I wish to exhibit a specimen of mediastinal lipoma. This specimen was taken from a moderately fat, middle-aged, male subject encountered in the dissecting room. No history of the case could be obtained, but the immediate cause of death seemed to have been acute lobar pneumonia of the right lung. The tumor was a large, lobulated lipoma. It sprang by a pedicle about 10 cm. broad from the tissues of the anterior mediastinum. The pedicle ramified from this point in many directions, involving the parietal pericardium, passing up along the bronchi, trachea, and great vessel, partly surrounding the descending aorta, and infiltrating the diaphragm. In all of these locations there were diffuse bands or small, lobulated masses of fat tissue. At the base of the heart the subpericardial fat was moderately thickened. The main mass of the tumor consisted of five distinct lobules of fat tissue, each about the size of a goose-egg, loosely attached to one another by broad pedicles. These were packed together in the lower part of the left pleural cavity, occupying rather more than one-half of this space. The lungs seemed to have gradually accommodated themselves to their contracted quarters, and did not show the ordinary evidences of compression. Both lobes of the left lung were about equally diminished in volume. There was moderate fat invasion of the myocardium in a few places, but the heart-muscle cells were not fatty. Microscopically the tumor had the structure of fetal fat tissue.

Dr. Osler: I should like to add a word in regard to the point of puncture in pericardial effusion. I agree with Dr. Fitz that the left costoxiphoid angle is in many cases the preferable point. Some fifteen or sixteen years ago I made a series of observations in the Philadelphia Hospital, in post-mortem, in reference to that very point as to whether there was any danger of puncturing the liver and relation of liver to pericardium. In all instances

you could puncture most readily into the pericardial sac high up in the costal xiphoid, and I have done it in several cases with pericardial effusions. In case of tuberculous pericarditis with large effusion, the patient was a young lad; we had already tapped several places and had only a small amount of fluid; we got on a subsequent occasion the largest amount of fluid by tapping the costoxiphoid space. Naturally with a large exudate the liver is depressed; we can sometimes tap half-way down the xiphoid without danger of penetrating the liver or peritoneum. The point Dr. Fitz has brought up in reference to the place to tap I consider of great importance.

Another point to which I might refer is the frequency with which we let patients die with large pericardial exudates, more particularly in pneumonia. I have been recently going over some of the pneumonia records at Johns Hopkins, and there were at least four or five instances in which we should have tapped the pericardium, or had the pericardial sac freely incised. There were large masses of exudate which were not recognized in the first, as is frequently the case in the later stage of pneumonia. I think we should use a small hypodermic needle to determine the presence of fluid. It makes no difference if you do puncture the ventricle, it never does any harm; in fact, the effect of puncture is sometimes stimulating.

Dr. Williams: Allow me to direct attention to the importance of fluoroscopic examinations as an aid in the diagnosis and treatment of pericardial effusion. I question very much whether there is any rule which will apply to all cases, but the fluoroscopic examination would give an excellent indication for the best place to insert the needle in an individual instance. May I ask if such examination was made of this patient? Examination of the chest in obscure thoracic and some obscure abdominal diseases is hardly complete nowadays unless a fluoroscopic examination has been made.

Dr. Fitz: No fluoroscopic examinations were made.

Dr. Northrup: In connection with the stimulating effect spoken of by Dr. Osler, I should like to say a word. I had a case in hospital that clearly demanded aspiration. I put in the needle and got a little fluid. To the amazement of all the needle wagged a little every time the heart beat, and it was not at all amusing. Immediately after the use of the needle, however, the patient appeared better. Within four hours the temperature dropped 2.5° and recovery followed. The puncture apparently determined an improved condition, which was marked, and recovery was rapid.

Dr. Forchheimer: I am not so cheerful about the results of putting a needle into a pericardial sac, especially in children. I saw one child of eighteen months, in whom I made the diagnosis of pericarditis with effusion. I

put in a needle to the left of sternum, drew off 2.5 cm. of fluid. The condition again returned and again I repeated the operation. In four hours after the second puncture the child was dead. At the autopsy we found that the right ventricle had been injured. I am sure that the rule put down by Dr. Williams is the correct one as far as the place of entrance is concerned. The place of puncture must be decided upon by the nature of the effusion and the quantity contained within the pericardial sac. For diagnostic purposes a hypodermic syringe should always be used. In all cases the cardiohepatic angle gives us distinct indications when the puncture should be made.

Dr. Peabody: As to the desirability of tapping in these cases of massive pericardial exudate which have been so common in connection with pneumonia in the past few years, in the first place it is a matter of interest to know how very different in type pneumonia is, taking one year with another. A year ago our cases of pneumonia in New York were very commonly associated with pericarditis with a massive fibrinous exudate, which would not have been detected by the insertion of any ordinary needle. In many cases diagnosis could not have been confirmed or treatment applied through any needle; and it has seemed to me, too, that the removal of the fluid that could be got away by ordinary tapping would not have contributed to the patient's welfare. It seems to me a rather safer rule in regard to the use of therapeutic measures, either of the needle or tapping, in general to wait until there are distinct evidences of impairment of cardiac function in consequence of exudate, then to remove, if one can. In many cases of unmistakable pericardial effusion, absorption occurs without any assistance from us. I do not think it very judicious either to rely on tapping by hypodermic needle as a means of making the diagnosis, or in routine fashion to tap every pericardium because there is effusion there. As a complication of pneumonia, particularly, there is such a dense mass of exudate as to render such tapping futile.

Dr. Northrup: My patient was not a child, but a 'longshoreman. I consider Dr. Forchheimer's point was well made.

Dr. Rotch: The pericardium has heen tapped in the fifth interspace to the right of the sternum with perfect success quite a number of times in children. The advantage of tapping in this interspace to the right of the sternum is that it would be very unlikely that even a much enlarged heart would be touched in this area, provided that the point chosen for introducing the needle is 3 or 4 cm. from the right edge of the sternum. Under these conditions it seems to me that it is wiser to first endeavor to get fluid at this point, as it is by no means a safe procedure, in children at least, to touch the heart when seeking for fluid.

Dr. Fitz: The failure to discover suspected fluid by tapping the pericardium, even in the xiphisternal space, should not discouarge further explora-

tion. I have tapped in this space with a negative result, and, after the death of the patient, a large quantity of fluid was found encapsulated by fibrinous adhesions. It seems, therefore, of distinct practical importance that one should not be contented with the negative result of exploratory puncture when the clinical evidence suggests the presence of pericarditic exudation. Exploratory incision should follow and the finger be inserted into the pericardial sac with the hope of destroying adhesions and enabling fluid to escape.

FEVER IN CHRONIC ENDOCARDITIS.

By JOHN S. THACHER, M.D.,
OF NEW YORK CITY.

The mechanics or physics of cardiac valvular lesions have been very thoroughly studied and discussed, but, except in a certain group of cases which have been called malignant or ulcerative or infective, the other clinical features of the malady have been very generally neglected, though French[1] has written a most interesting article on the course of fever in certain cases of endocarditis. It is certainly forced and arbitrary, far from scientific, and hardly at all helpful—perhaps misleading—to divide cases of chronic valvular lesions into the two groups, the purely mechanic and the malignant. I have frequently been impressed in the wards of the hospital by cases of chronic endocarditis without evidence of complications, in which the fever has been a striking symptom, but in which the course of the disease could in no sense be called malignant. It may be suggested that these febrile cases without evidences of secondary lesions are infective, a suggestion which may represent the truth, but which in the present state of our bacteriologic knowledge is largely theoretic and hardly helpful. In the hope of learning some facts as starting points for a partial clearing up of this subject, I have gone over the records of all the cases admitted to the Presbyterian Hospital between April, 1897, and March, 1905, which were put down as endocarditis either primary or secondary, including those called malignant endocarditis.

The total number of histories studied was 1093, or, viewing the different histories of a patient admitted more than once as making

[1] The Practitioner, 1904, vol. lxxiii. p. 753, The Temperature and Course of Infectious Endocarditis.

but a single history, 972. Of these 71 were discarded either because they were evidently fresh and first attacks (9 cases), or because the patient's stay in the hospital was so brief that the records were quite incomplete (41 cases), or because on reading the histories and records of autopsies the diagnosis seemed not to have been justified (21 cases).

This leaves 901 cases, which I have divided into five groups:

1. Those in which the temperature did not exceed 100°, 316 cases.

2. Those with a temperature exceeding 100°, and in which there were rheumatic articular symptoms, 131 cases.

3. Those with a temperature exceeding 100° and showing petechial or other hemorrhagic eruptions, 23 cases.

4. Those with a temperature exceeding 100° and presenting clear evidence of complications other than articular rheumatism or hemorrhagic eruptions, complications which would readily explain the presence of fever, 207 cases.

5. Those with a temperature exceeding 100°, but without clear evidence of any complication sufficient to account for the elevation of temperature, 291 cases.

In these statistics patients admitted at different times have some of them been classed in more than one group.

In drawing these distinctions of temperature a rare or occasional passing of the limit was not considered.

1. In only 316 cases of the 901, that is about one-third, did the temperature remain below 100°. In these cases it is interesting to note that 168 (53 per cent.) gave distinct histories of previous attacks of rheumatism or chorea, and while in the hospital 28 (9 per cent.) had symptoms of articular rheumatism or chorea:

Mild rheumatism	14 cases.
Severe rheumatism	9 "
Chorea	5 "
	28 cases, 9 per cent.

There were also 4 cases showing petechial eruptions, and 1 with purpuric eruption.

It is interesting further to see that in many of these patients complications were observed either clinically or postmortem,

which might have been expected to produce more elevation of temperature, viz.:

Acute pericarditis	3 cases.
Dry pleurisy	6 "
Pulmonary tuberculosis	3 "
Pulmonary tuberculosis (doubtful)	3 "
Infarction of the lung	2 "
Tonsillitis	1 "
Parotitis	1 "
Cholecystitis	1 "
Chronic colitis	1 "
Infarction of the spleen	1 "
Chronic gastritis and pancreatitis	1 "
Periurethral abscess	1 "
Femoral phlebitis	1 "
Ulcers of legs	1 "
Hemiplegia	3 "

2. The patients who suffered with distinct symptoms of articular rheumatism while in the hospital, and whose temperatures ranged above 100° were 131 in number, 20 per cent. of the febrile cases. Of these, 109 (17 per cent. of the febrile cases) showed no further complications. Compare this percentage with the 9 per cent. of febrile cases which had symptoms of articular rheumatism. In a considerable proportion of these cases the rheumatic symptoms were slight and yet the fever was high, and one of the interesting facts elicited by this study is that patients with chronic endocarditis and with rheumatic symptoms in the joints may have a high degree of fever. Acute articular rheumatism by itself may of course produce high fever, but I believe from the study of these cases that chronic endocarditis with articular rheumatism is apt to be associated with a considerably higher degree of fever than is rheumatism without endocarditis, and that this should be borne in mind in estimating the seriousness of cases of markedly febrile endocarditis with joint symptoms.

These rheumatic febrile cases have been divided into three groups according to the elevation of temperatures, the dividing line being 101.5° and 103°.

In the 109 cases the fever was: (*a*) of the first degree (100.1° to 101.5°) in 42 cases; (*b*) of the second degree (101.6° to 103°) in 36 cases; (*c*) of the third degree (above 103°) in 39 cases.

In 4 additional cases there was chorea besides the rheuma-

tism, 2 with fever of the first degree and 2 with fever of the third degree; and in 1 case there was chorea without rheumatism, the fever being of the third degree.

The remaining cases gave evidence of other complications besides rheumatism.

3. Those showing petechial or other hemorrhagic eruptions and whose temperatures rose beyond 100° were 23 in number. In 13 of the cases the eruption was called petechial, in 10 hemorrhagic. Blood cultures were made in 12 cases, with negative results in 8 cases, positive in 4.

The micro-organisms found in these 4 cases were in 1 case the pneumococcus, in 1 case the streptococcus pyogenes, and in 2 cases the staphylococcus pyogenes aureus. All of these 4 cases with positive cultures died in the hospital.

The range of temperature in these cases and the high mortality are shown in the following table:

TABLE I.

Summary.	*Cases.*	*Deaths.*
1. Maximum temperature 100°–101.5° barring an occasional rise	2	1
2. Maximum temperature 101.6°–103°	4	3
3. Maximum temperature 103° or more	17	15
Total febrile cases	23	19

Total afebrile cases, 3. 1 died after leaving hospital.

Autopsies were made in 7 cases, all revealing an endocarditis of different degrees of severity (see Table III.); in 2 cases a focus of infection, in 1 a septic uterus, and in the other a pelvic abrasion.

4. The fourth group, in which there were complications other than articular rheumatism or chorea and hemorrhagic eruptions, and probably sufficient in themselves to have caused the elevation of temperature, were 207 in number, 32 per cent. of the febrile cases, 23 per cent. of all the cases.

The most frequent complications were lobar pneumonia, acute pericarditis, acute pleurisy, cerebral embolism, thrombosis or hemorrhage, pulmonary tuberculosis, acute tonsillitis, phlebitis, typhoid fever, colitis, and bronchopneumonia.

TABLE OF COMPLICATIONS IN THIS GROUP.

	Cases.	Temperature. 100.1°–101.5°	101.6°–103°	Over 103°
Rhinitis	1	...	...	1
Tonsillitis	12	2	6	4
Laryngitis	1	1		
Influenza	1	1		
Otitis media	3	1	1	1
Mastoiditis	1	...	...	1
Acute pleurisy	22	4	5	13
Empyema	3	...	2	1
Cancer of the pleura	1	...	...	1
Lobar pneumonia	37	...	...	37
Bronchopneumonia	6	...	2	4
Pulmonary tuberculosis	13	5	2	6
Acute pericarditis	30	3	5	22
Gastroenteritis	1	...	...	1
Colitis	6	3	1	2
Hypertrophic cirrhosis of the liver	1	...	...	1
Cholecystitis	1	...	1	
Cancer of the peritoneum	1	...	1	
Purulent pyelitis	1	1		
Nephritis, acute exacerbations	4	3	...	1
Uremia	1	...	...	1
Abortion	2	1	...	1
Carcinoma uteri	1	...	...	1
Gonorrhea	2	...	...	2
Mastitis	1	1		
Meningitis	1	...	...	1
Tumor of the brain	1	...	...	1
Cerebral embolism, thrombosis, or hemorrhage	23	8	2	13
Delirium tremens	1	1		
Superficial ulcers and gangrene	6	3	...	3
Abscesses and cellulitis	10	2	2	6
Erysipelas	3	...	...	3
Phlebitis	9	3	2	4
Periostitis	1	...	...	1
Fracture	1	...	...	1
Typhoid fever	7	...	...	7
Malarial fever	6	...	...	6
Incision of the leg	1	...	...	1
Phlebotomy	3	1	...	2
Aspiration of chest	6	...	4	2
Tapping abdomen	4	...	4	

These four operations at the end of the list are included because they were in each of these instances followed by a sharp and unexpected rise in temperature.

5. We now come to the cases in which there was an elevation of temperature beyond 100° without any marked complication to account for it. Such cases I find amount in number to 291. It occurred, then, in 32 per cent. of our cases. It is not to be

assumed that this percentage would hold with all cases of chronic endocarditis outside of as well as within the hospitals, for undoubtedly those who are feverish are, if other things are equal, more likely to come into the hospital than those who have no fever. Still the large proportion of 32 per cent. is certainly striking.

In none of these cases were there symptoms of articular rheumatism during the patients' stay in the hospital.

I have divided them into three groups, as in the last series, according to the degree of fever, the dividing lines being 100°, 101.5°, and 103°.

Cases with fever above 100° without apparent cause, (*a*) 100.1° to 101.5°, 172 cases, 19 per cent. of all our cases; (*b*) 101.6° to 103°, 66 cases, 7 per cent. of all our cases; (*c*) above 103°, 53 cases, 6 per cent. of all our cases.

(*a*) These cases, 172 in number, gave no frank signs of major complications, but in a few instances there were suggestions of slight complications as follows:

Infarction of the lungs	12 cases.
Bronchopneumonia	2 "
Tuberculosis	7 "
Pleurisy	8 "
Pericarditis	1 "

In 1 of the cases cultures made from the blood developed pure growths of staphylococcus pyogenes aureus. There were slight indications of pleurisy in 1 case, but no other indication of complications.

In 15 cases of this group (V. A.) autopsies were made, and in 11 the autopsy as well as the clinical picture awarded nothing which would have been apt to produce fever unless simple passive congestion of the viscera can do so. In 4 cases, however, though the signs and symptoms during life suggested no complications, some were found postmortem as follows:

1. Acute colitis, acute pleurisy, and cerebral thrombosis.
2. Pleurisy with effusion.
3. Cholecystitis, portal thrombosis, and acute peritonitis.
4. Lobar pneumonia and acute pericarditis.

(*b*) The cases with fever reaching 101.5°–103° without apparent cause number 66.

(V. B.) Of these cases 8 came to autopsy. In only 1 of these was any lesion found outside of the heart likely to cause fever. In that case there was the appearance of a chronic dry pleurisy and a thrombosis of one vertebral artery.

(*c*) The last 53 cases with temperatures above 103°, as they are the most interesting, I have divided into three sub-groups:

(1) Cases in which this high degree of fever was not long continued, 14 cases, 1½ per cent. of all our cases.

(V. C. 1.) In 5 of these autopsies were made, and in only 1 was any complication found which would be likely to raise the temperature. In that case there was an acute pericarditis.

(2) Cases in which there was a suggestion of moderate complication, 16 cases, 2 per cent.; these suggestions pointed toward:

Possible consolidation in	4 cases.
Possible tuberculosis in	1 "
Infarction of the lung in	7 "
Pleurisy in	1 "
Acute bronchitis in	2 "
Infarction of the spleen in	1 "

In only 1 of these cases was there an autopsy. In this no complication was discovered postmortem beyond general passive congestion of the viscera and dropsy.

(3) Lastly, cases in which this high temperature was prolonged without any symptoms or signs indicating complications, 23 cases, 2½ per cent. Autopsies were made on 7 of these, and in only 2 were there found complications likely to produce fever. In these 2 cases there was

1. General miliary tuberculosis.
2. Acute meningitis.

The above figures show the frequency of fever in chronic endocarditis, the frequency of its various degrees, and its comparative frequency under certain conditions. The following table (Table II.) shows the frequency of certain clinical features in some of the groups into which we have divided the cases. We can here see whether a rheumatic history, urinary changes, enlargement of liver, etc., are more frequent in the afebrile cases, in the rheu-

matic febrile cases, or in the febrile cases without rheumatism or other complications.

Regarding the mortality among the patients of the different groups, the reports from those who left the hospital alive have been very incomplete, having been received from only about one-fourth of them, but I will give the statistics as far as they are available (Table III.).

We notice here that the highest immediate mortality is in the febrile cases with petechial or other hemorrhagic eruptions. Next, but far less fatal, are the febrile cases with important complications other than rheumatism, and the febrile cases without complications. Far the mildest as regards mortality are the afebrile cases and the febrile cases with rheumatic symptoms. It is surprising to see that the latter, the febrile rheumatic cases of chronic endocarditis, are less deadly than the afebrile cases. This may be due to the fact that the pains drive into the hospitals patients whose hearts are not very badly off.

From Table IV. we can see that the clinical course of the fever is not always determined by the character of the endocardial lesion. Of the 21 cases in which autopsy discovered large vegetations, with or without ulceration, 4 did not go above 100° and 4 did not go above 101.5°. The 3 cases in which sclerosis with ulceration of the valves was noted were all afebrile. Of the 36 uncomplicated febrile cases in which autopsies were made, only 3 had large vegetations (these 3 showing ulceration), 7 had small vegetations and sclerosis, 2 small vegetations alone, 16 marked sclerosis, and 8 slight sclerosis. Of the 13 autopsy cases with high fever, above 103° without complications, 2 had large vegetations with ulceration, 2 small vegetations with sclerosis, 1 small vegetations alone, 5 marked sclerosis, and 3 slight sclerosis, showing the much greater frequency of the sclerosis than the vegetative changes seen in cases with high fever.

Table V. shows the results of cultures from the blood.

TABLE II.

	I.		II.		III.		Cause of fever not explained.								
							V. A.		V. B.		V. C.[2]		V C. subdivided.		
	Temperature not above 100°, 316 cases, 35 per ct. of total.		Cases complicated with rheumatism, 131 cases, 14 per ct. of total.		With fever, and petechial or hemorrhagic eruptions, 23 cases, 2.5 per ct. of total.		Max. temp. 100° to 101.5° barring occasional higher rise, 172 cases, 19 per ct. total.		Max. temp. 101.6° to 103° cause of fever not being clear, 66 cases, 7 per ct. total.		Total.		Max. temp. of 103° or more, cause of fever not being clear, 53 cases, 6 per ct. total.		
													1[3]	2[4]	3[5]
	Cases.	Per ct.	Cases.	Per ct.	Cases.	Per ct.	Cases.	Per ct.	Cases.	Per ct.	Cases.	Per ct.	Cases.	Cases.	Cases.
Previous history of rheumatism	168	53	98	75	16	69	88	51	34	54	...	...	14	16	23
Single attack or a few mild attacks	53	17	14	10	8	35	39	23	11	16	6	...	2	0	4
Repeated attacks or very severe attacks	75	24	60	45	5	21	36	21	15	22	16	...	5	6	5
Repeated severe attacks	20	6	20	15	3	13	11	6	6	8	4	...	2	2	0
Chorea	20	6	4	3	0	0	2	1	2	3	2	...	...	1	1
Total	168	53	98	75	16	69	88	51	34	54	28	...	9	9	10
While in hospital 28 (9 %) had symptoms of articular rheumatism or chorea	28	9	131	100											
Mild rheumatism . .	14	4.5	87	66											
Severe rheumatism . .	9	2.9	40	30											
Chorea	5	1.6	4	3											
Erythema multiforme .	...	...	1	0.7											
Erythema nodosum . .	...	...	1	0.7											
Tonsillitis	...	...	1	0.7											
Total	28	9	134[1]	100											

Urine:															
Albumin less than 5	136	43	53	38	14	60	82	47	32	48	24	...	9	5	10
Albumin 5 or more	50	16	12	9	5	21	56	32	17	25	19	...	4	7	8
Casts hyaline and granular	106	34	29	22	15	65	100	58	37	55	28	...	7	10	11
Casts hyaline and granular with other varieties or with blood	18	6	2	1	1	4	6	3.5	4	5					
No record of urinary examination	11	...	1	0.7	...	...	3								
Leukocytes:															
Less than 10,000	9	...	8	...	2	...	11	...	4	...	5	...	0	2	3
10,000 to 14,000	10	...	14	...	4	...	19	...	5	...	6	...	1	2	3
15,000 to 19,000	5	...	9	...	5	...	7	...	6	...	9	...	2	3	4
20,000 to 29,000	4	...	4	...	4	...	4	...	4	...	1	...	0	0	1
30,000 or more	2	...	1	...	0	...	...	...	1	...	3	...	0	2	1
Liver:															
Probably enlarged	23	7	9	6	2	9	23	13	6	8	4	...	2	0	2
Edge less than 2 inches below	24	8	6	4	2	9	17	9	6	8	5	...	1	1	3
More than two inches below border of ribs in the right mammillary line	45	11	4	3	5	21.8	47	27	23	34	13	...	5	6	2
Spleen:															
Probably enlarged	7	2.3	3	2	0	0	5	2.9	1	1	2	...	...	1	1
Clearly enlarged	9	2.8	6	4	6	26	15	8	6	9	5	...	1	...	4
Minor complications:															
Fluid in pleura	32	10	7	5	2	9	27	15	16	23	12	...	3	5	4
Signs of congestion	106	34	30	22	2	9	89	52	26	39	21	...	9	5	7
Blood-stained sputum	3	9	3	2	2	9	...	...	4	5					

[1] Three of these cases had two rheumatic complications.

[2] V. total, 291 cases, 32 per cent. of total.

[3] Fever not high long.

[4] Suggestion of slight complication.

[5] Above 103°. Prolonged high fever with no indication of complication.

TABLE III.

	Total cases.	Died in hospital.	Per cent.	Autopsies.	Known to have died after leaving.	Known to be still living.
I.	316	51	16	19	17	29
II.	131	16	12	7	4	23
III.	25	20	80	7	1	0
IV.	207	83	40	35	8	10
V.	291	117	40	36	19	23
V.a	172	60	34	15	14	20
V.b	66	27	40	8	2	2
V.c	53	30	56	13	3	1

TABLE IV.—The Valves at Autopsy.

	I.	II.a	II.b	II.c	Total II.	III.	IV.a	IV.b	IV.c	Total IV.	V.a	V.b	V.c	Total V.	Total.
Large vegetation with ulcerations	2	...	...	3	3	2	...	...	1	1	1	...	2	3	11
Sclerosis with ulceration	3	...	...	...	...	...	...	...	...	...	...	...	...	...	3
Large vegetations without ulceration	1	1	...	...	1	1	2	1	4	7	...	...	...	...	10
Small vegetation	1	...	...	...	...	2	...	...	...	...	1	...	1	2	5
Small vegetation with sclerosis	5	1	1	...	2	2	1	1	9	11	3	2	2	7	27
Marked sclerosis of valves	4	...	...	1	1	...	...	3	4	7	5	6	5	16	28
Slight sclerosis of valves	3	...	...	...	...	...	3	1	5	9	5	0	3	8	20
Total	19	2	1	4	7	7	6	6	23	35	15	8	13	36	104

I. Temperature not over 100°.
II. " over 100°, with joint symptoms.
III. " over 100°, with petechial or other hemorrhagic eruption.
IV. " over 100°, with complications explaining fever.
V. " over 100°, without complications explaining it.
a. " 100.1° to 101.5°.
b. " 101.6° to 103°.
c. " over 103°.

TABLE V.—Blood-culture Cases.

Groups.	Negative.			Positive.					
	Died.	Living.	Total.	Strept.	Staph.	Pneu.	Died.	Living.	Total.
I.	0	0	0	...	...	...	...	...	0
II.	6	11	17	...	...	...	...	...	17
III.	7	1	8	1	2	1	4	...	12
IV.	6	5	11	...	1	2	2	1[1]	14
V.	3	7	10	1	2	2	5	...	15
V.a	0	0	0	...	1	...	1		
V.b	0	4	4						
V.c	3	3	6	1	1	2	4		
Total	22	24	46	2	5	5	11	1	58

Four of these 58 "blood-culture" cases appear in two groups, and 1 case appears in three, reducing the actual total to 52.

[1] Discharged almost moribund. Staph.

The cases whose temperature curves follow, with very brief statements of the main features of the cases, will show the great variety to be met with in the course of fever in chronic endocarditis. In some it is an extreme intermittent fever (the septic type); in others it has long waves, it may be of a week or several weeks (typhoid type); in others it is fairly continuous, and in others again extremely irregular. Instances will be seen where high and prolonged fever of whichever type is followed by improvement, occasionally by a long period of fair health.

From this review we see that:

1. A large proportion of hospital cases of chronic endocarditis, even when uncomplicated, have fever.

2. In many this fever is of high degree and long continued without apparent cause.

3. Neither the presence nor the degree of fever in these cases follows strictly the variety or degree of endocardial lesion.

4. The febrile cases with hemorrhagic eruptions are extremely fatal.

5. The febrile uncomplicated cases are about as fatal as the cases with marked complications and very much more fatal than the afebrile cases.

6. Nevertheless, some of these cases with high and prolonged fever get better.

7. The line marking off the group of malignant endocarditis is very uncertain.

8. The rheumatic febrile cases of chronic endocarditis are as favorable as the afebrile cases, or possibly more so.

Case I.—R. G., male, aged eighteen years. Never had rheumatism, but often tonsillitis. Dates heart symptoms from six years ago when tonsils were removed. Dyspnea and forcible heart action since then. In hospital five months. Long waves of typhoid-like fever from three weeks to a few days in length and occasional isolated high shoots. Four loud murmurs. A little hypertrophy of the heart. No Widal reaction, six tests. Leukocytes, 13,000, 16,000. Blood cultures negative three times. No typhoid bacilli obtained from urine. Spleen never palpable. In good health since July, 1904—that is, for the last nine months—working fairly hard as cook. No symptoms except a little pain below apex of heart. The murmurs still distinct.

Case II.—B. B., female, aged fifty years. History of considerable rheumatism. Heart symptoms twenty-two years. In hospital one month. Irregular intermittent temperature for two weeks, after that below 100°. Leukocytes below 7000, counted four times. No complications. Discharged in much improved condition.

Case III.—J. B., female, aged twenty-two years. History of slight rheumatism. Dyspnea and edema for four months. In hospital two months with prolonged high intermittent fever. Loud mitral systolic and aortic diastolic murmurs. No chills or sweating. No malarial organisms found (two examinations). Leukocytes, 18,000, 7000, 11,000. On admission petechial spots, rather old, and murmurs over both lower extremities. Comfortable most of the time while in the hospital. Blood culture negative. No complications except three large intestinal hemorrhages in one day. Discharged improved.

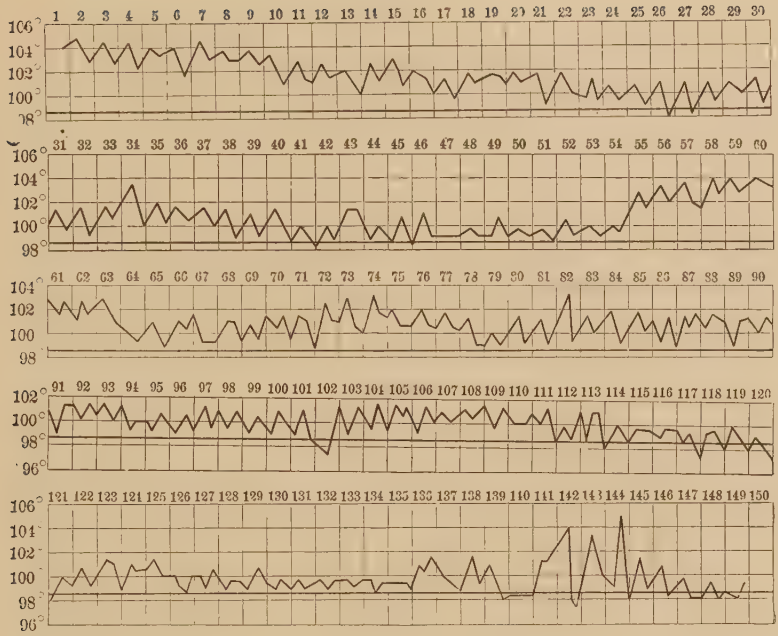
Case IV.—A. M., female, aged twenty years. No previous history of rheumatism; palpitation for one year. Two weeks before admission to the hospital vaccination took; one week later chilly. On admission a double murmur was heard at the apex, and later a diastolic at the base and the pulse became "Corrigan." The heart was much enlarged. She was in the hospital about six weeks; the first four days the temperature ranged between 102° and 103.6°, and then gradually came down to normal at the end of three weeks. The liver and spleen were a little enlarged. The leukocytes were 8000, 18,000, and 8000. Two blood cultures were made with negative results. The Widal test was negative on three trials. Ten months later she returned with a gastrointestinal disturbance and the same cardiac condition, except that the mitral presystolic murmur was not heard. She was in the hospital two weeks, but only on the first day did the temperature exceed 99.5°. The leukocytes were 5000.

Case V.—L. T., female, aged thirty years. History of severe rheumatism, but none in hospital. Mitral presystolic and systolic murmurs. Albumin, 30 per cent. No complications. In the hospital five weeks with frequent irregular shoots of fever, though only four times above 102°. The last two weeks only once above 100°. Discharged not improved.

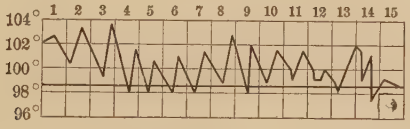
Case VI.—C. K., male, aged ten years. History of considerable rheumatism, but none while in the hospital. Cardiac symptoms for five years. In hospital five weeks with irregular, moderate, intermittent fever. There were no complications. He seemed to improve, but died two weeks after leaving the hospital.

Case VII.—I. H., female, aged thirty-nine years. No history of rheumatism. No rheumatism while in the hospital. In hospital two months with irregular, usually moderate elevation of temperature. No complication. Aortic and mitral systolic murmurs. Died. Autopsy showed sclerotic valves, especially the mitral and tricuspid. No complications to explain the fever.

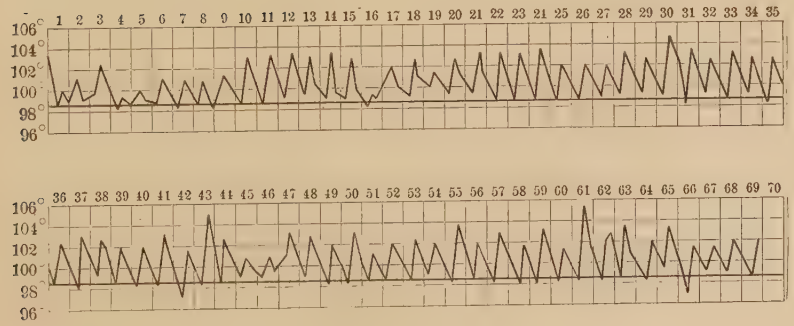
Case I.



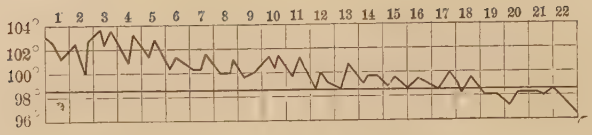
Case II.



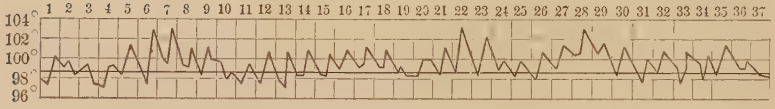
Case III.



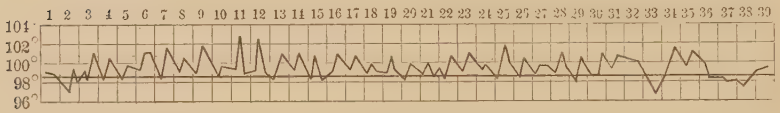
Case IV.



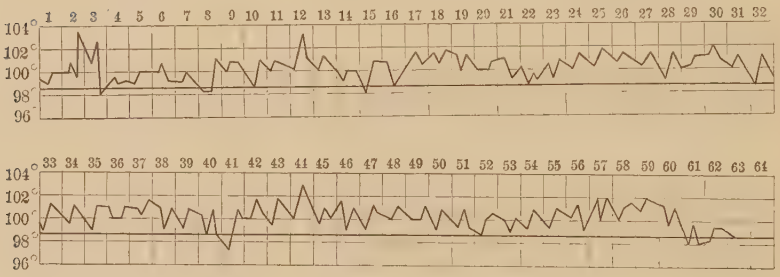
Case V.



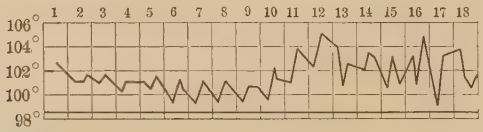
Case VI.



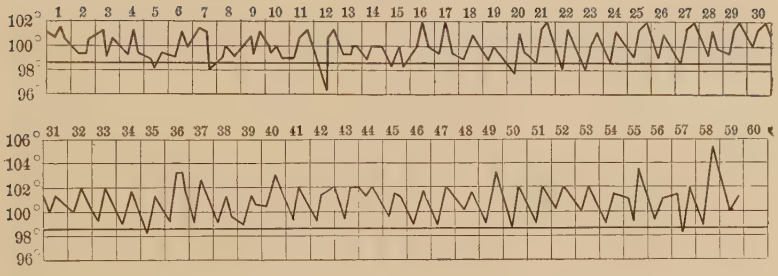
Case VII.



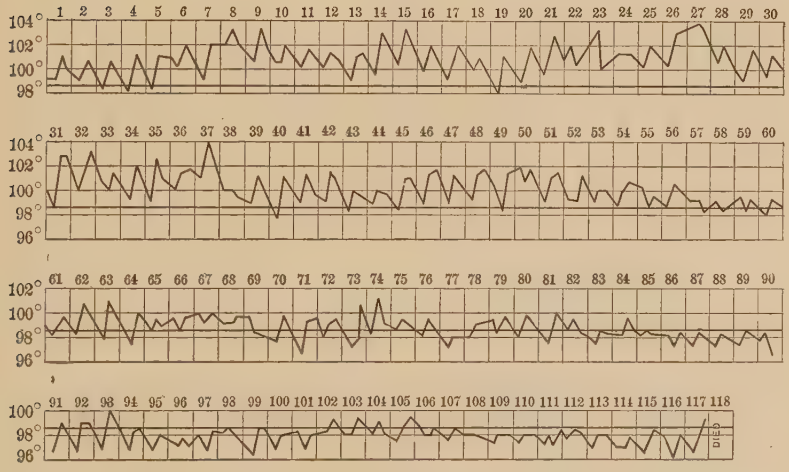
Case VIII.



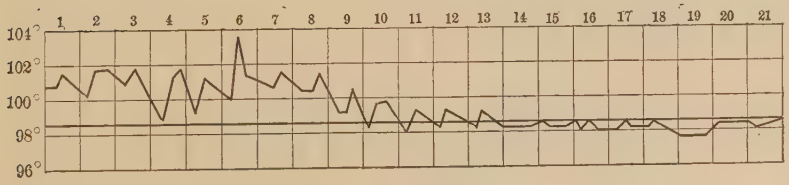
CASE IX.



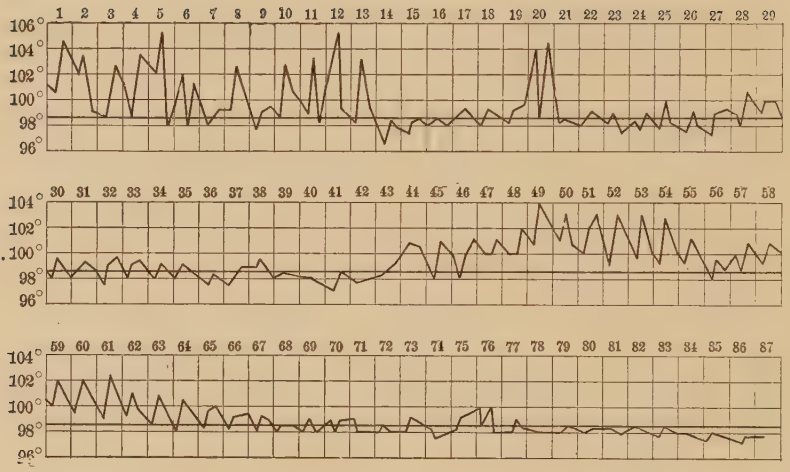
CASE X.



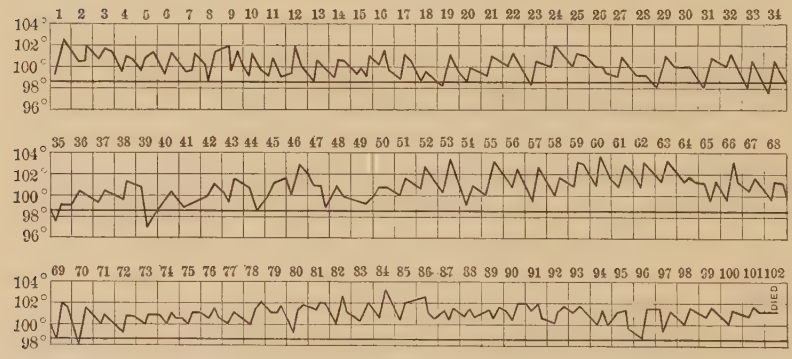
CASE XI.



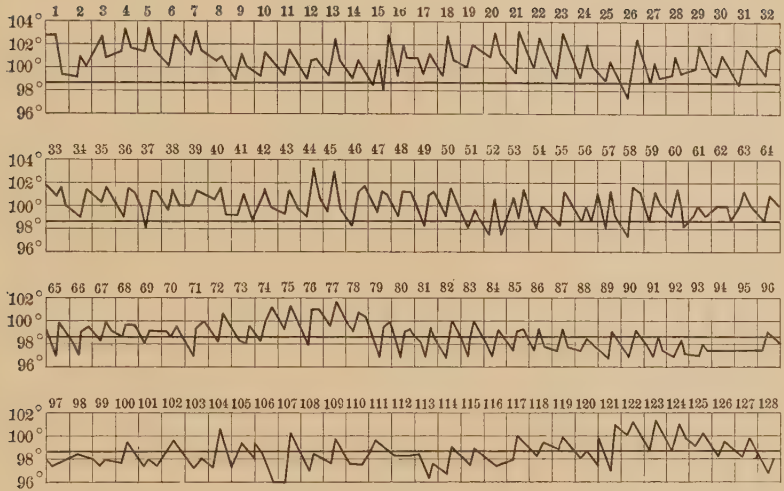
CASE XII.



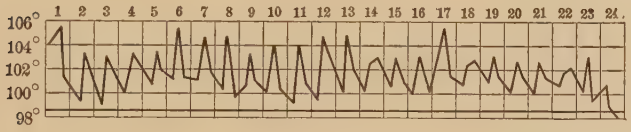
CASE XIII.



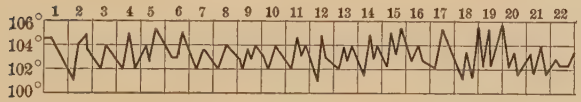
CASE XIV.



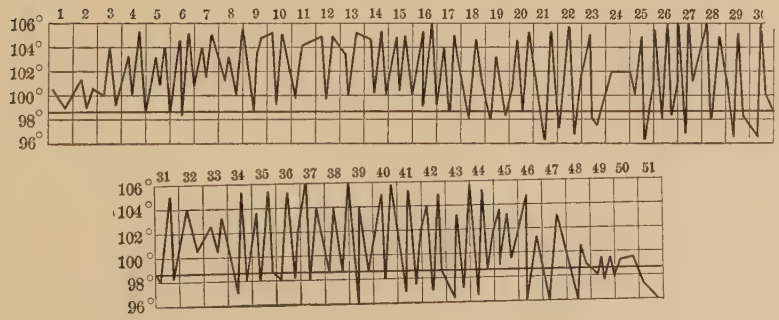
CASE XV.



CASE XVI.



CASE XVII.



Case VIII.—E. L., female, aged thirty years. No history of rheumatism. In hospital two and one-half weeks. Aortic systolic and mitral systolic murmurs. Albumin up to 30 per cent. Temperature uneven, with remissions generally moderate. No complications. Discharged unimproved.

Case IX.—M. B., female, aged nineteen years. Only doubtful history of rheumatism. No previous cardiac symptoms. In hospital two months with moderate, rather irregular, remittent and intermittent temperature. No Widal reaction. No tuberculin reaction. Leukocytes, 7500. Urine normal. No complications. Discharged unimproved.

Case X.—M. W., female, aged fifteen years. History of considerable rheumatism. In hospital four months, with very irregular, remittent temperature the first two months, after that rarely fever. Albumin up to 30 per cent. Symptoms apparently the same during the febrile and the afebrile periods. No complication while in hospital. Died. No autopsy.

Case XI.—J. K., female, aged forty-five years. No history of rheumatism. Cardiac symptoms for two months. In hospital three and one-half weeks. Mitral systolic murmurs. No joint symptoms. Moderate, irregular temperature for ten days, and normal for ten days. Discharged improved.

Case XII.—B. M., female, aged eighteen years. History of considerable rheumatism. Cardiac symptoms for two years. No rheumatism in hospital. Mitral presystolic and systolic murmurs and a diastolic at apex. No complications. In the hospital three months. During the first three weeks, very irregular, high, intermittent temperature; later, a remittent wave of about three weeks. The rest of the time mostly normal, including the last three weeks in the hospital. Discharged and was in fair health for three months, but died seven months after leaving the hospital.

Case XIII.—L. J., female, colored, aged thirty-nine years. Cardiac symptoms eight months, well-marked rheumatic history. In hospital three months. Temperature of long, irregular waves with marked remissions. Mitral systolic and presystolic murmurs. Albumin up to 60 per cent. No complications. Died. No autopsy.

Case XIV.—M. B., female, aged twenty-five years. History of much rheumatism. In the hospital four months. Double murmurs at apex, later double murmurs at base. Albumin up to 25 per cent. Numerous crops of purpuric eruptions the last two days before death, but the temperature, which was irregular and remittent the first two months, went below 100° most of the last two months. The autopsy showed much sclerosis of aortic, mitral and tricuspid valves, with only slight granulation.

Case XV.—W. B., female, aged nineteen years. History of slight rheumatism, none in the hospital. In the hospital four weeks, with a high, fairly regular, deeply remittent temperature. Mitral systolic and presystolic murmurs. An attack of hemiplegia two days before admission. No petechiæ. Blood culture obtained growth of pneumococcus. Autopsy. No fungating

masses on the valves, but a fringe of vegetations on the mitral valve, and extending to the adjacent ventricular surface. Pneumococci were obtained from autopsy cultures.

Case XVI.—A. C., male, aged thirty-four years. In hospital twenty-four days with a petechial eruption and high, not markedly remittent temperature. History of slight rheumatism. Cardiac symptoms only a few days before admission. Systolic murmur at apex. Edge of spleen palpable. Widal test negative, many trials. Blood cultures negative, three times. Died. Autopsy showed a "wet brain" and slight thickening of the mitral valves.

Case XVII.—E. G., female, aged thirty-eight years. History of slight rheumatism, also some slight joint pains while in the hospital. No previous cardiac symptoms. In the hospital seven weeks, with very high intermittent fever, usually two waves daily. Double murmur at base, systolic at apex. No petechiæ. Autopsy. On one aortic cusp a polypoid mass-like granulation tissue, with surface slightly irregular, but without ulceration. Infarction of the spleen.

DISCUSSION.

Dr. W. G. Thompson: I should like to ask Dr. Thacher whether he regards the presence of a murmur of some sort as a necessary diagnostic feature? I was much impressed with an article published five or six years ago in the *Medical and Surgical Report of the Presbyterian Hospital.* It was a compilation of more than 700 cases of autopsy findings, with the clinical memoranda of murmurs, giving the ratio wherein one might be mistaken on both sides, which proved to be 1 case in 7—*i. e.*, in 1 case in 7 of valvular lesions were present at autopsy and no murmur had been heard; and the reverse was proved that 1 case in 7 diagnosed as endocarditis showed the presence of murmurs and on autopsy no lesion. The ratio I have quoted was carefully compiled, and the cases occurred in the service of different physicians attached to the hospital; so I think personal equation may be fairly eliminated.

Dr. Kelly: If I have understood Dr. Thacher correctly, he has stated that cases of chronic endocarditis are commonly divided into two classes: (1) those in which the mechanic defect is the predominating factor, and (2) those in which manifestations that we usually ascribe to malignant endocarditis are in the foreground. Between these he has endeavored to build up an intermediate third class—cases in which fever occurs at irregular intervals, fever for which he has been unable to find any adequate explanation. As I view the subject the matter is one of broad general principles, and if we have a clear conception of the nature of endocarditis the explanation of the fever in the cases, such as Dr. Thacher describes, is quite near at hand. There can be no question that endocarditis, aside from the cases due to arteriosclerosis and allied processes, is an infection provoked under varying circumstances

by different micro-organisms. The facts that endocarditis is almost always a secondary process arising in the course of divers infections; that the infective agent reaches the endocardium by way of the circulation; and that in many cases bacteria may be cultivated from the blood stream; in a word, that bacteremia is a factor in all cases, suggests that there is little essential difference between acute endocarditis and other manifestations of so-called septicemia. The clinical features also are so nearly alike that the most astute clinician is often at a loss to say whether or not in a given case the bacteremia has implicated the endocardium, though, of course, in most cases this is easily enough recognized. Acute endocarditis, then, is a toxemia or bacteremia (arterial pyemia it has been called), the involvement of the endocardium being, as one might say, accidental, and in some respects of comparative insignificance. The arthropathies, urticarias, erythemas, and embolic phenomena are common to both; and the difference between the two, though sometimes well marked clinically, is one of degree and distribution only. The endocarditic lesions, however, often persist as latent foci of infection after other manifestations of the original infection have subsided, or the damaged endocardium, being of reduced vitality, is unduly susceptible to later infections—such as may be well disposed of by other parts of the body. The irregular attacks of fever in chronic endocarditis, such as Dr. Thacher has described, are merely evidences of recurring infection, of the relighting of slumbering foci, a fact well recognized by the Germans in their designation recurring endocarditis. As a matter of fact I have never looked upon attacks of fever in chronic endocarditis as unusual; they are part of the clinical course, of the natural history, of the disease, and as such should be correctly recognized and interpreted.

Dr. J. K. Mitchell: There are a few cases in my practice every year of moderate fever of very long duration, accompanying chorea, the chorea being often of but moderate degree. These present no evidence of any rheumatism, have neither sign nor symptom of heart disease, and yet there is fever sometimes lasting five or six weeks.

In the past four or five months there have been, I think, six such cases, and in the previous season as many more, but only one of these eleven or twelve cases developed any distinct signs of endocardial disease, and even that was not until the patient had had three weeks of continued fever, when the pulse suddenly became unduly high, and the development of an acute endocarditis followed, with final recovery.

The point I wish to make is that there is often in chorea fever without any signs of endocarditis, and yet my impression is that the fever must be due to a degree of endocarditis so mild that it shows no sufficient or characteristic symptoms.

The results have usually been good except for the exhaustion due to the long continuance of the fever, the duration of which is much greater than in ordinary cases of acute chorea in which one sometimes sees a febrile attack,

probably rheumatic in origin. My emphasis lies, however, in the cases mentioned, on the point that there were no signs of endocarditis.

Dr. Jacobi: There is or need be no murmur in an endocarditis when the ulcerations are on the insertion of the pectinate muscles, a short distance from the edge of the valves. On the other hand, there are many cases where we are apt to make the diagnosis of endocarditis because there is a systolic murmur, and very frequently a systolic mitral murmur; they are not cases of true endocarditis, but of myocarditis. Such a systolic mitral murmur sometimes extends all over the precordium and upward. It will get better for months, the murmur never disappearing, but brought out on the very slightest exertion. These are cases of myocarditis; they are diagnosticated by the fact that there is no enlargement or hypertrophy following the original murmur. I think that these cases are very frequent. I am sure that everyone here has seen them, and that I do not say anything that is new in connection with the subject, but I thought I would direct attention to it again. We should not make a diagnosis of endocarditis of some duration unless it has resulted in a dilatation and hypertrophy. When they or one of them are not found it is safer to diagnosticate a myocarditis.

Dr. Tyson: I should like to call attention to the relation between chronic mitral endocarditis and petechial eruption without fever. I have at present under my care a girl, twenty-four or twenty-five years old, with chronic endocarditis, and frequently recurring petechial eruption, and a subnormal temperature. One of its interesting features is the sudden appearance of these eruptions, which are confined to the legs, coming on in the course of an hour or two, and especially invited by the upright position. The eruption disappears more slowly than it appears. They are less apt to occur when the patient is in bed than when she is up. They disappear also much more rapidly when the patient is put to bed. The condition is associated with an inveterate but not very marked anemia, hemoglobin of 70 per cent. contrasted with one of 50 per cent. on admission, which it seems impossible to increase above 70. The point which has interested me, and on which I would like to have information, is the relation of the endocardial lesion to this suddenly appearing petechial eruption. The petechiæ occurring in malignant or so-called ulcerative endocarditis have been regarded as embolic in origin. This can hardly be said to be the case with the petechiæ in my chronic case referred to.

Dr. Preble: In a compilation of this sort it is important to distinguish between the different forms of chronic endocarditis. That form which occurs especially in children is always the result of bacterial infection, and recurrence of the infection often, in a mild degree and with prolonged fever, could not be a matter of surprise. A second form never seen in children, but found frequently in older people, is not due to the implantation of bacteria upon the valves, but is the result of the same changes going on in the valves,

which in the vessels are known as arteriosclerosis. In such cases there is no fever, and any effort to determine the frequency of fever in chronic endocarditis must give incorrect results unless this distinction is allowed for.

Dr. Vaughan: There is one point I want to speak about: that is the remark Dr. Thacher made concerning the temperature. If there is one thing established about the bacterial poisons it is that all bacterial poisons lower the temperature. There is no exception so far as I know to this statement. The exact effect upon the temperature will depend upon the kind of germ with which the individual is infected and the rapidity with which the poison in that germ is set free. We all know that one of the clinical signs for distinguishing between tonsillitis and diphtheria is the temperature. If there is a temperature of 104° or 105°, ten to one it is a case of tonsillitis. If there is a temperature of 100° or 101° or below, the chances are that it is diphtheria, and in diphtheria the lower the temperature the more dangerous it is. The cases of subnormal temperature are the cases that always die. The reason why the low-temperature patient dies is the rapidity with which the bacterial poison is set free. We have adopted a word used by musicians to express our meaning, that is the "tempo," with which the bacterial poison is liberated, and this is measured more clearly by the fall in temperature than by anything else. It is not, therefore, surprising to find that in the cases where the temperature did not go above 100 the death rate was the highest. The point I want to make is, the more rapidly the bacterial poison is liberated the lower the temperature.

Dr. Osler: I should like to show a remarkable chart illustrating the form of fever in chronic endocarditis. I think the fever in endocarditis, that is, in chronic endocarditis, you may have a slight recurring fever, which is then due and anatomically explained by the little vegetations which are so common on the old sclerotic valve; then you have secondary acute malignant endocarditis which rapidly proves fatal, or you may have a severe endocarditis which looks as if it might prove fatal, but in which recovery takes place in the course of a month, and one of our patients, a man who has been under observation for thirteen or fourteen years, has had three or four such severe attacks of fever in connection with his mitral endocarditis, and he has recovered from each one of them; in one of the attacks he had a temperature of 105° to 106°. I want to call attention to a form of chronic fever associated with chronic vegetative endocarditis, lasting in some cases an entire year, nothing but fever and the signs of a progressive endocarditis occurring and going on to a fatal termination. Here is an instance in point (showing a long temperature chart). This temperature record covers exactly a year within two days, in which the patient had a fever every day. I saw the case twice with Dr. Mullen, of Hamilton, and she had a fever; there were no embolic features, but a mitral murmur. Nothing but that. The question was whether we could attribute the protracted fever to the ordinary mitral murmur. I saw

her first in October, again in April. It was the same girl, the same room, the same fever. I wondered could it possibly be this ordinary murmur with the little enlargement of her heart which could account for all this. I am sorry that I only found this chart a few days ago. The heart was sent to me; she had a chronic vegetative endocarditis, the mitral segments encrusted, some of the chorda tendineæ eroded away, without much erosion or ulceration. I have had a series of such cases. Dr. Ward reported one at the last meeting of this Association. They may be mitral or aortic; they may continue four months, or seven months, or thirteen months; thirteen months is the longest I have seen a case. The interesting thing is that the fever dominates the whole picture. The cardiac symptoms are quite slight at first. These are the cases that Bristowe and Lancereaux, and some of us here, regarded as of malarial origin. The case Dr. Ward reported he thought at first was of malarial origin. Dr. W. W. Johnston, of Washington, reported a couple of cases. I believe it is quite different from other cases of endocarditis. It cannot be very malignant. You cannot apply such a term to a case that lasts more than a year. The last case was in a physician who had seven and a half months' fever. I had known him for years; he had a mitral lesion, and it was not difficult for me to determine that it was his old mitral trouble, but on he dragged through the spring and summer and died last November, and the same sort of condition of his valves, chronic vegetations, some encrustation of the chorda tendineæ, erosion; and Dr. MacCallum, who made the autopsy, found staphylococcus and streptococcus, but they must have been of a very mild and mitigated variety.

Dr. Kinnicutt: I should only add a word to the discussion on these cases with fever. They do not all die. Some of them get well. In the past year I have had two cases under my observation where there was long-continued fever such as Dr. Osler describes, fever, fever, fever, and nothing else beyond a slight mitral murmur. In one case the fever lasted seven months; in the other case it lasted five months. During all this time an increase of the murmur was not noted, and to-day the patients are well, although the murmur still persists.

Dr. Thacher: In reply to Dr. Kelly I should say that it was impracticable to do otherwise than accept as cases of endocarditis those which were so labeled by the physicians in attendance after they had treated them in the hospital. I could not go behind the returns except in the four cases which, as I have said, I threw out.

In reviewing the cases I noted those which presented superficial evidence of arteriosclerosis. It is, of course, important to make a distinction of such cases, as has been pointed out by Dr. Preble, but in reporting this collection of cases it was impracticable to make too many subdivisions.

RHYTHMIC LATERAL DISPLACEMENT OF THE HEART AS A SIGN OF UNILATERAL PLEURITIC EXUDATE.

By CHARLES LYMAN GREENE, M.D.,
OF ST. PAUL, MINN.

In August, 1902, the writer called attention to a rhythmic lateral displacement of the heart, synchronous with respiration, as a sign of unilateral liquid exudate in a pleural cavity. More extended observation has tended to confirm the statements made in that preliminary report, and has served also to show the value of the sign in differential diagnosis. Opportunities have offered for investigating, by combined fluoroscopy and auscultatory percussion, twenty cases of simple pleurisy with effusion, two of empyema, one of pneumothorax, two of subdiaphragmatic abscess and two of malignant disease of the lung and pleura associated with small pleural exudates. Many cases representing the ordinary routine of office and hospital work, embracing a variety of cases of cardiac and pulmonary disease, as well as normal chests, have been carefully examined in relation to the cardiac displacement observable in respiration. Of the miscellaneous cases only one showed any marked lateral movement, this being a dilated heart with mitral lesion and pericardial adhesion. In the cases of malignant disease of the pleura, one sarcomatous and the other carcinomatous, neither showed any marked degree of lateral displacement in respiration. In a case of left-sided subdiaphragmatic abscess from caries the heart was somewhat displaced to the right and upward, but there was no lateral movement in respiration. In the case of pneumothorax the heart was displaced far to the right, the maximum impulse being just within the right nipple line, but no lateral movement of the heart was perceptible in respiration, nor could any move-

ment be expected in such cases because of the shallow breathing and slight or paradoxical diaphragmatic movement.[1] All of the cases of simple effusion examined showed the rhythmic lateral displacement in varying but marked degrees, the least movement being observed in a case of massive effusion of the right side, in which instance the heart became very freely movable after the withdrawal of two pints of fluid.

In the cases of empyema observed the cardiac excursion was like that seen in simple effusions. In all of these cases the heart seems to move upward as well as outward, as might be expected from the nature of its attachment and the forces exerted upon it. An upward and downward movement has long been recognized, and it would seem that this upward movement may have caused observers to overlook the coincident lateral displacement associated with unilateral pleuritic exudate. The change in the position of the heart is not only to be observed by means of the fluoroscope, but, according to my own experience, is quite readily determined by auscultatory percussion, if not by ordinary percussion, and in some instances of right-sided effusion the lateral shifting of the apex beat is evident on mere inspection. In cases of effusion into the right cavity little difficulty is experienced in outlining the left border of the heart by the usual methods.

In left-sided effusions the displacement of the heart and its radius of movement is greater, but auscultatory percussion, or the fluoroscope, is necessary for the accurate determination of the right border. In order to secure the deep respirations necessary to the best definition recourse must sometimes be had to the exhibition of morphine. In the course of his work the writer has failed to observe any cases of liquid pleural effusion in which there was no lateral movement of the heart. He has also been unable to confirm the correctness of the observations leading to the statement that in many cases of this sort the diaphragm is absolutely paralyzed, and in some instances forced downward, so as to actually bulge into the peritoneal cavity. Even in a case of massive purulent effusion of long standing, the diaphragmatic excursion was marked. Its position is low, of course.

He further ventures to take issue with the statements made by

[1] Kienböck's diaphragm phenomenon.

some writers upon the *x*-ray, to the effect that the extent of persistent cardiac dislocation in liquid effusions cannot be accurately determined without the use of the fluoroscope. In nearly every instance of this sort dislocation of the heart to the left was determined without difficulty by ordinary percussion. In the case of displacement to the right auscultatory percussion was found to give results that bore well the test of fluoroscopic examination. In determining the exact extent of the rhythmic excursion of the displaced heart in respiration, however, auscultatory percuss on is absolutely necessary in the absence of fluoroscopic examination because of the lung movement and expansion of the unaffected side. It seems strange that a phenomenon of this kind should escape notice for so long a period, though no stranger than the many instances of a similar sort in the history of medicine. Indeed, if one considers the forces acting within and about the pleural cavity and the peculiar relation of the heart to the pleural sacs, one cannot avoid the conclusion that movement of that organ from side to side must occur in the presence of a unilateral liquid exudate, unless the amount of fluid is trifling or the diaphragm paralyzed. In such cases the liquid is in a cavity containing an elastic and compressible lung, and has a powerfully muscular and movable floor acting automatically and, by abdominal reinforcement, in a piston-like manner. The cavity is limited laterally by a chest wall quite rigidly resistant to internal pressure, yet capable of expanding and contracting at will. The amount of force exerted by an effusion is well shown by the prompt and effective compression exerted upon the lung of the affected side, quite apart from the other factors, causing lung shrinkage, and we can readily understand its effect under the law of hydraulics upon the yielding partition represented by the pericardium, its surrounding tissues, and the movable organ enclosed within it. In inspiration the contracted diaphragm and raised ribs enlarge the thoracic cavity, the pericardium is somewhat tautened, the fluid column is lowered, and its pressure in part removed. The expanding sound lung exercises opposing pressure. At this time, therefore, the displaced heart tends to move toward the affected side. In forced expiration the abdominal muscles contract, the diaphragm rises, the pericardium is relaxed, the thoracic walls are contracted, the liquid column must ascend, lateral pressure is

increased, and the movable heart is forced away from the affected side and meets a lessened resistance from the unaffected lung. It would seem to follow that the maximum movement would occur in moderate-sized effusions, and this corresponds to the writer's observations. The following conclusions are offered:

1. A rhythmic lateral movement of the heart occurs in unilateral liquid pleural effusions of any considerable amount.

2. Such movement is most marked in medium-sized effusions.

3. The heart approaches the affected side in inspiration and moves outward in expiration.

4. The extent of movement is variable, but often amounts to two inches.

5. It may be measured by fluoroscopic examination, auscultatory percussion, or, in the case of right-sided effusions, by simple deep percussion of the free cardiac border, or in some instances by mere inspection of the apex beat.

6. Deep breathing, and especially forced expiration, are essential to the success of the maneuver, and to obtain this morphine must sometimes be administered.

7. Marked rhythmic lateral movement has not been found by the writer in pneumonia, tuberculous infiltrations of the lung, malignant disease of the pleura or lung, or in subdiaphragmatic abscess.

The writer sincerely hopes that these observations will be fully tested by his colleagues, and that this sign may prove of real value in the differential diagnosis of thoracic diseases.

ACROMEGALY ASSOCIATED WITH SYMPTOMS OF MYXEDEMA.

A REPORT OF PROGRESSIVE CHANGES IN A CASE UNDER OBSERVATION DURING A PERIOD OF EIGHT YEARS.

By CHARLES LYMAN GREENE, M.D.,
OF ST. PAUL, MINN.

In 1901 the writer brought the subject of this report before the American Medical Association, then in session at St. Paul.

At that time he presented the usual features of acromegaly plus (*a*) a condition of the hands and of the neck and shoulders not to be distinguished from myxedema; (*b*) predominating hypertrophy of the upper jaw, with marked separation of the teeth; (*c*) bilateral chronic synovitis of the knee-joints.

The original history of the case reads as follows:

L. G., aged twenty-five years; no fixed occupation; works at ice-cutting in the winter. Family history, past diseases negative. First symptom noticed (1896) was enlargement of the hands and feet and changed facial outline and expression. In the winter of 1898–99 he had swollen knee-joints, without marked pain or complete disability. The changes in the extremities progressed steadily until the summer of 1901; then the writer noticed an enlargement of the clavicles, scapulæ, and ribs. His condition in June, 1901, was reported as follows:

The hands and feet were enormous; the wrist and ankles free from inflammation, but bulky, thick, and in strong contrast with the forearms and legs, which, in the upper fifths of their length, were quite normal. The patient complained of languor and weakness, but had none of the severer vertical pains so common in acromegaly, nor did he complain of pain in the lumbar region or

limbs. There were no signs of disturbance of the special senses, nor of the nervous system. The skin throughout the larger portion of the body was nearly normal, and lacked the harshness of myxedema. The appearance of the face was especially interesting. There the skin was thickened and hypertrophied, though not rough. Deep furrows had formed over the frontal region, both upper and lower eyelids were thickened, and the ears appeared clumsy and tumid. The superciliary ridges projected, the nose was large and tumid, the nasal arch was prominent, the malar bones projected markedly, and the lower jaw, while not distinctly prognathic, was apparently enlarged, both from the angle to the symphysis and vertically. The upper jaw was enlarged, and the patient's attention had been called to that fact by the gradual separation of certain of the teeth and by the marked forward projection of the superior dental arch.

The enlargement of the upper jaw no doubt masked the changes in the lower jaw, depriving the case of one of the so-called typical signs of the disease. Both the upper and lower lids were thickened and clumsy, the tongue was large but not excessively so, the larynx was enlarged as well, and its cartilages were apparently the seat of hypertrophy. No deformity of the spine or chest existed, nor were there any marked changes in the clavicle or the scapulæ. The fundus oculi was normal and the hands presented the usual spade-like appearance, with the sausage-like fingers and square, flat nails, showing longitudinal striation. The radiograph demonstrated the remarkable enlargement of the bones, both in length and thickness. The process seemed to involve the lower fifth of the adjacent long bones and of their overlying tissues, which presented the same typical characteristics as the hands. There was at first no marked enlargement of the great toe, such as has been described in several instances, but later photographs show marked hypertrophy. Neither the hands or feet were the seat of pain, nor were their movements much restricted. A feature of special importance, however, was the marked increase in bulk of the overlying tissues, which presented the appearance and yielded the sensation of a hard edema, indistinguishable from myxedema.

Aside from the presence of dulness over the manubrium, suggesting a persisting thymus gland, the internal organs seemed to be normal. The condition of the knees was merely that of chronic

FIG. 1

Showing enlargement of the bones of the hand and the radius and ulna.

FIG. 2

Showing enlargement of the bones of the great toe.

synovitis. Since his first appearance in clinic he had undergone some dentistry for the correction of the dental deformity and unsightly gaps due to the enlargement of the upper jaw. He suffered from a cystitis of mild, recurrent type, due to a neglected urethritis, but is able to work as a baggage hand or truckman.

Since 1901 no changes in the hands, head, or legs have been noticeable, but without thyroid treatment the myxedematous swelling has wholly disappeared, and the clavicles, scapulæ, and ribs have steadily increased in size. Though still able to do light work, he suffers from occasional syncope and tires easily. The urine yields the usual evidences of a cystitis, easily corrected but promptly recurring. Coincident with the shrinkage of the hypertrophied soft parts we have observed marked diminution of the thyroid gland. The case is again presented because of the following features:

1. Disappearance of the myxedematous element.
2. The coincident shrinkage of the thyroid.
3. The shifting of the seat of abnormal bony growth.
4. The long period of observation.
5. Continued predominance of hypertrophy of upper jaw as compared with the lower.
6. Present predominant hypertrophy of the great toe.

DISCUSSION.

Dr. Cohen: The association of myxedema and acromegaly is extremely interesting. Dr. Greene's cases bring to mind one I exhibited before the Philadelphia County Medical Society some years ago, in which this association was present. The myxedema disappeared under the administration of thyroid gland, but the acromegaly persisted until death, which probably resulted from the pressure of a pituitary tumor. There was bilateral temporal hemianopsia.

EPIGASTRIC LINEA ALBA HERNIA AS A LITTLE RECOGNIZED SOURCE OF ABDOMINAL PAIN AND OF GASTRIC SYMPTOMS.

By D. D. STEWART, M.D.,
OF PHILADELPHIA.

The occurrence of hernia in the linea alba above the umbilicus—hernia most frequently of small size and often only apparent on minute examination, and its importance as a source of gastric symptoms—has received far too little attention by both clinician and surgeon. The fact that a nodule of adherent omentum or of preperitoneal fat united to the peritoneum by a pedicle, a protrusion often so small as only to be discovered on the closest inspection or by careful palpation, may produce and continue symptoms simulating gastrointestinal disease, that gastralgia, enteralgia, gastritis, gastric ulcer and cancer, gallstone disease and the like have been erroneously diagnosed, and that the hernia, the cause of the symptoms, has long escaped observation renders the topic of considerable clinical interest.

My attention was first directed to the subject about ten years ago through a case in my service in the Polyclinic Hospital, the first, so far as I know, that I had seen, certainly the first I had recognized. The patient, a Russian Hebrew, was brought to the hospital with a severe attack of abdominal pain, and was seen in the out-wards by Dr. T. S. K. Morton and myself. He gave a history of a long-existing, unrelieved, gastrointestinal disorder, the chief symptom of which was recurring colic. Examination of the abdomen disclosed a small hernia in the linea alba above the umbilicus, which was acutely sensitive to touch and which was evidently the cause of the symptoms. The case made a deep impression, and I have since had in mind the likelihood of the

occurrence of this form of hernia as a source of obscure abdominal pain, and almost invariably, as a routine procedure, have looked for it in the examination of patients with gastrointestinal symptoms. The knowledge of its occasional occurrence and that existing—it may be the source of symptoms otherwise inexplicable—has been of considerable service to me. In the past decade in hospital work I have seen a number of these cases, and have had five in private practice. I wish now to relate briefly several recently observed instances which have about them points of clinical interest. I shall then refer to a few others bearing on these:

Case of small supraumbilical hernia of the linea alba, causing recurring, severe gastralgia:

E. A. F., slender build, nervous temperament, aged twenty-seven years, clerk, consulted me July 1, 1904. He had been subject to spells of colic for several years, an attack lasting often four to five days, with intervals of from a few days to several weeks between. Pain had origin in the epigastrium, and thence spread over the whole abdomen. An attack was more apt to occur after eating, especially if he overindulged. The pain might occur without relation to eating, and apparently was very little influenced by the character of the food. Overeating, causing indigestion, would aggravate the frequency and severity of the attacks. There was more or less bowel flatulency; the bowels were quite regular without laxatives; had often been freely purged during an attack, with the idea of decreasing its severity; pain then was rather aggravated than ameliorated. There was no loss of flesh; poor appetite; he got very little fresh air and no out-of-door exercise. Smoked eight to ten cigars daily; was somewhat addicted to venereal excess and late hours. moderate alcoholic indulgence.

Physical Examination. Slender built young man; handles yarns in his business; no blue line, no history of plumbism. Nothing abnormal in chest, save slightly irritable heart (tobacco). Abdomen rather thin, though firm walled. In the erect posture and in recumbency there was evident only on careful scrutiny, but easily apparent to the palpating finger, a very small nodule in the linea alba, the size of half an ordinary-sized pea, 1½ inches above the umbilicus. It was firm to the touch, very sensitive to even delicate palpation; it was without impulse on coughing, and irreducible. The stomach was normally placed, liver and spleen outline normal, left kidney not palpable, lower pole right kidney barely so, and no hernia elsewhere.

The patient was immediately told that the small nodule was the probable cause of his attacks, and operation suggested, but he was absolutely opposed to this, and desired medical treatment, especially since his family physician, a surgeon as well, was then in Europe.

Several examinations made to determine the condition of the stomach, showed mucous, subacid gastritis.

July 2, 1904, an hour after 60 gm. bread, 250 c.c. water, 45 c.c. removed. Largely ropy mucus; filtrate amber; total acidity, 47; Günzberg, very faint response; Toepfer, 25; starch, imperfectly transformed.

Second test of this day: Fasting, two hours; same meal as above, 80 c.c. removed; more remaining, as subsequent lavage showed. Considerable amount of ropy mucus; total acidity, 38; Günzberg, faint reaction; Toepfer, 20; starch, imperfectly transformed.

7th. Three hours after half-pound sirloin steak, potato, two rolls, half glass of milk, small amount only removed. Tube blocked by food and debris, and ropy mucus; total acidity, 50; no response to Günzberg or to Toepfer solution.

Second test: Urine clear, amber, acid; specific gravity, 1030; albumin, normal trace; glucose, absent.

Microscopic Examination. Nothing noteworthy.

Patient was seen frequently in July; epigastric hernia always as above described, though less sensitive later to palpation. Adherent omentum noted in case history as the evident exciting source of the pain, attacks of which, perhaps, were maintained and aggravated by the condition of the digestion and patient's habits of life.

The following treatment was instituted: Discontinue tobacco; very little venery; more fresh air; diet and habits to be generally regulated; daily morning stomach douching; hot sodium bicarbonate solution, followed by cool, physiologic salt solution; glass of Carlsbad water, drunk after lavage; occasional castor-oil capsule at night. Before meals, extract cannabis indica, 6 mg. ($\frac{1}{10}$ gr.); extract nux vomica, 0.02 mg. ($\frac{1}{4}$ gr.); anesthesin, 0.19 gm. (3 gr.); after meals, pancreatin. If gaseous distention is marked at night, when attacks commonly originate, naptholated charcoal. The attacks had been very frequent before consulting me, and there was commonly daily epigastric pain. On the foregoing treatment there was immediate improvement. The pains were less frequent and severe, and it was noted September 15th that none whatever had occurred since July 22d. The cannabis indica-anesthesin combination was only continued for a short time; the pancreatin, steadily.

September 20th. Examination stomach contents, an hour after 60 gm. bread, 200 c.c. water, moderate amount removed, well solved; no mucus; total acidity, 45; Günzberg, trace; Toepfer, 20. Nitromuriatic acid, nux vomica and gentian ordered before meals. No pain from July 22d until October 7th. Then attack at 11 P.M.; very severe abdominal cramp, lasting about fifteen minutes; doubled him up; no nausea or vomiting; bowels regular, freely opened. Had been walking three to four miles after breakfast to his business place. He was again smoking to excess, and habits otherwise unhygienic.

October 17th he reported pains and indigestion as formerly. Patient has relapsed into old condition; operation again urged, without result; improvement again followed care in diet, attention to general health, and resumption of morning lavage. No attacks from September 13th until November 30th; then presumably due to marked indiscretion in diet.

January 11 and 12, 1905, severe attack each night; dietetic indiscretion. Hernia not apparent to eye, and but slightly to finger; much gaseous distention of the bowels. For a considerable time prior to this date sensitiveness had ceased about the hernia, and no pains occurred again until January 25th. He then reported that for several days he had had repeated severe attacks of colic. Exquisite sensitiveness was now present on palpating the ring of the hernia; the hernia itself was not evident to the finger. Immediate necessity for operation was now made apparent to the patient and his family, to which Dr. Steinbach, his family attendant, to whom I now again sent him, agreed. Dr. Steinbach had seen the patient with me three months before, but in view of family opposition to surgical interference, had preferred to postpone this.

Operation was done by Dr. Steinbach, January 27th. The following is the doctor's report as to the findings: "The hernia was occasioned by a somewhat oval opening in the linea alba, about one-half inch in its vertical and one-quarter inch in its transverse diameter. The peritoneum (sac) was adherent to the integument, and a portion of the omentum, in the shape of radiating strands, was adherent to the sac, and, therefore, practically to the skin. I excised an elliptic portion of the integument with the adherent peritoneum sac, ligated the adherent portion of the mesentery, cut it off in front of the ligature, and closed the opening by through-and-through sutures, and separate sutures of the linea alba. There was no real strangulation, because the sac could quite properly be said to have had no neck, but the adhering of the mesentery caused it to thicken and form the strands which I mentioned, and this practically gave rise to the pains."

The patient made a good recovery, and at the present writing (May 8th), he reports no attacks since the operation. Flatulency, which had been a marked symptom prior to operation, has now disappeared.

It is very evident how such a condition could originate attacks of abdominal pain, which, when the pain habit had thus been established, could be aggravated and continued by the gastric condition present, and the patient's unhygienic habits lowering nervous tone and accentuating the existing neurotic inheritance.

In the following case, so far as I can ascertain, the hernia had never been regarded in its consideration. The physician—an abdominal surgeon as well—whom the patient had seen prior to consulting me, although he had examined the abdomen, informed me that he had not noticed the hernia. In this case the most prominent symptom, apart from very evident neurasthenia, is a nervous disturbance of digestion, characterized by persistent, rebellious flatulency. I regard it as likely that the hernia, through

long-continued reflex disturbance of the gastric functions, has been a factor in the production of the gastritis present, since no history of abuse of the stomach is in evidence.

M. M., Hebrew, aged fifty years, merchant; recently seen. Stomach trouble for many years, chiefly nervous in character; gaseous distention of the stomach and bowels constantly present; sensation of fulness and discomfort after meals; bowels regular; appetite good, occasionally "crampy" pains. He is about ten pounds below his best weight; habits always good; never abused stomach; on the contrary, overcareful. Nervous and hypochondriac. Has been to many physicians in Europe and in this country without relief of symptoms.

Physical Examination. Chest, nothing abnormal. Abdomen, epigastric hernia sensitive to touch, the size of half a small flattened shellbark, evident in linea alba about an inch above the navel. Marked gaseous distention of the abdomen. This, he states, has been apparent for years. Stomach slightly dropped; inflation shows inferior border below umbilicus; no dilation. (Inflation and water tests.) Liver, spleen and left kidney normally placed; right kidney palpable on deep inspiration, but not abnormally loose.

Urine, clear; light amber; acid; specific gravity, 1008; albumin and glucose, absent. Microscopically, nothing noteworthy.

Examination Stomach Contents. Cleansing lavage at 9.30 A.M.; 9.45 A.M., 60 gm. bread, and glass of hot water; at 11 A.M., 50 gm. bread, glass of hot water; at 12 noon, stomach empty; 100 c.c. thickish contents; much ropy mucus; total acidity, 55; Günzberg, strong reaction; Toepfer, 30; starch digestion, fair.

The following day cleansing lavage at 8.30 A.M.; 9.45 A.M. half-pound steak, 2½ oz. bread, 12 oz. weak tea. Three hours after finishing eating, emptied stomach; 200 c.c. well solved; fluid; large amount ropy mucus; amber filtrate; total acidity, 100 (litmus); Günzberg, absent; Toepfer, 53.

Despite the presence of mucus, acid gastritis with atony, and the absence of direct symptoms resulting from the hernia, I regard the latter largely as the cause of the symptoms. The hernia had existed at least sixteen years, about the time of the onset of the ailment. It is soft to the touch, at times a slight gurgle is evident in it, as if it might be a gastroepiplocele; it is irreducible. The patient has been under observation two months; the gastritis received active treatment; morning lavage with hot soda solution; followed by cool physiologic salt douche; silver nitrate douche, or silver vitellin employed two or three times weekly for a month. Menthol valerianate for the control of nervous belching used without result, as was naphthol and charcoal, to discover if the flatulency was of fermentative origin. Bitter tonics and nervines were administered, all of which are usually helpful in the condition present. Although there was considerable improvement manifest in the gastric condition as concerns diminution in mucus production, and lessening in atony, the flatulency, nervous belching and general gastric discomfort persisted. Despite urging, the patient refuses operation.

The following case was referred to me by Dr. B. Segal for an opinion. The doctor stated in his note of reference that the patient "had been suffering from pain and distention of the stomach for a number of weeks. Treatment gives him temporary relief only. I suspect malignant trouble."

A. G., Hebrew, aged fifty years; attacks of cramp-like pain of great severity in epigastrium; through to the back; present for at least five weeks; then with onset of pains, at the height of their severity, he had spells of vomiting, which now no longer occur, although pains still as pronounced.

Examination of abdomen disclosed a small, fixed, epigastirc hernia in the linea alba, a little below the xiphoid cartilage; it has a circumference about that of a silver quarter of a dollar; it is soft, and suggests a gastroepiplocele. Pain has origin in this spot, and then radiates through either hypochondrium to the dorsal region. The hernia is exquisitely sensitive to touch; there are no other gastric symptoms; appetite is good, and bowels regular.

The patient was returned to the doctor, with an opinion that the hernia was undoubtedly the cause of the trouble. The patient refused operation.

In these cases the hernia was small. In the first it was barely apparent to the eye, while in cases 2 and 3 it was, though small, fairly evident on inspection, with the patient in the erect posture. It is cases such as these which are the most troublesome, since the apparent triviality of the protrusion, even if it does not escape recognition, often does not suggest itself to the physician as a likely source of the malady.

The occurrence of epigastric hernia, the majority of which is in the linea alba, was originally described by Garengeot[1] under the name of gastrocele. It furnishes somewhat less than 1 per cent. of all varieties of hernias,[2] and is far more common in the male than the female. It is more usual in adult life than in infants or children, and its occurrence in the majority of cases is believed to be due to a congenital or acquired defect in the fascia[3] of the linea alba, as a result of which trauma and strain produce a slight diastasis of the recti. Into this either a nodule of subperitoneal fat (preperitoneal lipoma united by a pedicle to the peritoneum) makes its way; or, more commonly, a portion of omentum,* which rarely may be accompanied by a portion of the

* A comprehensive account of the pathologic anatomy of epigastric hernia has been given by H. A. Lathrop (Boston Medical and Surgical Journal, February 25 and March 4, 1897). Lathrop points out that as in the epigastric area there are no preformed openings, the hernia must make its way through a rent in the tissues of the linea alba and that a common point of origin is that between the umbilicus and the xiphoid cartilage, at which the sound ligament and paraumbilical veins leave the abdominal wall, on their passage to the liver.

small intestine, and more rarely by stomach. A strain, as by heavy lifting, or some unusual form of exercise, violent vomiting or coughing, producing a sudden rise in intra-abdominal pressure, is the probable exciting cause. These forms of hernia, of which one is the rule and of which two are unusual, whether preperitoneal fat or omental, through their nerve connections, and especially through their attachments to the subjacent structures, and to the stomach* or liver and their fixation by adhesions about the orifice of the ring and its under surface, rarely fail to originate early symptoms after their appearance. There may be no apparent fixation of the hernia at the ring, a portion of omentum being intermittently incarcerated and producing recurring pains only through its presence. With relaxation of the recti in recumbency the hernia may disappear, as in a case recently observed. The small separation in the linea alba, or immediately to one side, apparent on careful palpation, then furnishes the clew to its existence. The symptoms are commonly as described in the foregoing cases and in those to be related, and are usually referred to the stomach, whence a diagnosis of some form of gastric disorder—gastritis, gastralgia, ulcer, or even gastric carcinoma—is made by the unwary, or the case may be looked upon as one of gallstones.

I recently saw a case through the kindness of Dr. Deaver, in which the symptoms—severe recurring attacks of gastralgia and enteralgia, with vomiting and debility, and neurasthenia of high grade—had been previously attributed to gallstones by a well-known surgeon. And the diagnosis was concurred in by a clinician of wide experience. On this account, in the operation for the removal of the epigastric hernia by Dr. Deaver, the gall-bladder was also explored, but found entirely free from disease.

In this case there was slight reason for confusion, the hernia was large, and although it has existed for a long time without special direct symptoms, the recurring and persistent attacks of severe colic following immedialety after exercise involving unusual physical strain, indicated the source of the pain. The patient was of neurotic temperament, and had become the subject of hysteroidal attacks while suffering from nervous prostration, the result of mental overapplication and family worry. Later, when in fairly good physical condition, an attack of intense abdominal pain immediately followed unusual muscular strain, as above stated, and these attacks had continued (and entirely replaced the former hysteroidal seizures) with increasing frequency for

* It is especially the pull or drag of the omentum on the stomach in these cases which tends to originate the gastric symptoms.

eight years. Morphine was required for their relief. The character of none of the seizures suggested gallstone disease; they were distinctly gastralgic and enteralgic; and if not a result of the hernia, could only be regarded as of neurotic source. An interesting feature was the persistent attacks of abdominal pain for some months after operation, and then their gradual cessation; their long existence before the removal of the hernia having, in a neurotic subject, established a pain habit not easily broken. The case in this respect seemed analagous to those of Jacksonian epilepsy, in which a too tardy, though thorough removal of a coarse brain lesion does not readily cure the firmly established fit habit. The protrusion was still evident for some months after operation, but now has not been apparent for a long while, although its former site is still extremely sensitive to slight pressure. The attacks of pain diminished in severity following the operation, but did not finally cease for some time. None has now occurred for over five months.

Lathrop[4] related an instructive case in which attacks of jaundice occurred, complicating abdominal pain, the result of an epigastric hernia, and caused the diagnosis of gallstones to be made by several physicians.

The patient, when a rugged boy of eighteen, fell upon a sharp-pointed stick, injuring the epigastrium. Collapse followed and for some weeks local pain. Six years later sharp pains in the epigastrium, with other gastric symptoms, especially after eating, appeared and continued with varying severity. For ten years from this time he suffered from moderate gastric symptoms, accompanied by pain and tenderness in the epigastrium. Twenty years before Dr. Lathrop's report the attacks of pain and vomiting became more frequent and severe, and then a small, tender swelling was noticed above the umbilicus. This tumor increased until it became the size of a fist, but was commonly reducible with coincident alleviation in symptoms. Five years later, in addition to the attacks of pain and gastric symptoms, coincident with the appearance of the hernia, he began to have chills, elevation of temperature, and a marked degree of jaundice. The attacks were without periodicity, from a week's interval to occasionally three months, provided the hernia was retained in position, although persistent distress after eating and a dull ache and occasionally sharp pains in the epigastrium were noted. Inspection with the patient lying on the back showed nothing abnormal, except a little fulness of the skin in the median line, half-way between the xiphoid and the umbilicus, which became prominent on coughing, and when fully protruded formed a mass the size of a hen's egg. The mass could be reduced, except a small portion which was adherent to the ring. The ring admitted only the tip of index finger. Operation showed the omentum firmly adherent around the whole inner circumference of the ring, and continued inward toward the pyloric end of the stomach (greater omentum) and thence to the liver (lesser omentum) as a fairly firm band. On severing this from the ring it was found to contain the round ligament of the liver (obliterated umbilicus vein) and a portion of the falciform ligament and the great omentum.

Seven months after operation the patient was reported "entirely relieved of all his old symptoms, and only regrets that he was not operated on twenty years before."

Lathrop notes that jaundice has been recorded six times as a complication in epigastric hernia in cases in which at operation the gall-bladder and ducts were normal. The patients were operated on for presumed gallstones. "In all the cases there was an adherent omental hernia, the tension of which may have obstructed the gall-bladder at times."

Bergmann,[5] of Berlin, in a clinical lecture in 1894, stated that he had encountered more than a dozen cases of epigastric hernia "in which the best specialists of Berlin and Paris had diagnosed gastritis, gastric ulcer, and cancer, and had previously employed lavage, rigid diet, and other approved modes of treatment without result." Hernia in the linea alba had later been discovered, corrected, with a cure in each instance; and König,[6] in his text-book on surgery, relates similar instances.

In this particular, Davis reports a very interesting case, which for a number of years he and other physicians had more or less under observation, and in which he, throughout this period, without thorough examination, had treated for gastritis, presumably the result of alcoholism. The man had recurring attacks of very "intense gastric pain, vomiting, great nervousness, and cardiac depression. The ingestion of but a teaspoonful of water would aggravate his suffering and provoke vomiting. Morphin, hypodermically, alone gave relief. The seizures usually followed close upon the heels of debauches, lasted from three days to a week, when the symptoms disappeared as if by magic." But it was later noted that many of the seizures were dissociated with alcohol, and as he was rheumatic it was presumed by another attendant, and in a measure then coincided with by Dr. Davis, that the affection might have origin in "a rheumatism of the muscular fibres of the stomach." Some eight years after he had been first seen by Dr. Davis, but when he had not been for some time under the latter's observation, an abdominal examination by Dr. Davis disclosed a small hernia of the linea alba "not larger than a butter bean" about one and a half inches below the xiphoid appendage. Of the existence of this, the patient had been aware for years, and had been told by previous attendants whose attention had been directed to it that it was a small cyst and of no importance. Operation by Dr. Davis showed an adherent omentum continued in "the form of a band to a greater curvature of the stomach not far from the pylorus." There was no recurrence of the attacks, the patient making a complete recovery.

Aaron[7] relates a case in which the symptoms of presumed gastric catarrh had existed for four years. There were, with intervals

of freedom from symptoms, recurring attacks of nausea and vomiting and epigastric pain; anorexia, and a loss of twenty-eight pounds in four months, due to the persistent inability to retain food. The removal of an epigastric hernia, about the previous existence of which the patient was unaware, brought about a speedy recovery, with no return of symptoms in the lapse of five years.

W. H. Bennett,[8] in a clinical lecture entitled "Deceptive Abdominal Pain in Latent Hernia, Especially with Reference to the Surgical Aspect of Certain Cases of Indigestion," recites two very interesting cases of long-existing and improperly treated "dyspepsia," due to unrecognized epigastric hernia in the linea alba, and cured by their removal:

One, a woman, aged thirty-two years, had "for ten years been constantly a victim of very acute dyspepsia," as she described it. Cramp-like pain after food, especially that which was indigestible, was the most prominent symptom. She had consulted a variety of physicians, and by all had been treated for dyspepsia. Bennett, at the termination of an examination of the abdomen, and then somewhat accidentally, discovered in the linea alba, about halfway between the ensiform appendix and the umbilicus, a small, rounded, movable nodule, about the previous existence of which she or her former attendants had no knowledge. From this the pain had origin and radiated. Dr. Bennett remarks, as to the somewhat accidental discovery of the hernia, that he examined her as carefully as he could, and was bound to say he could at first find nothing that could account for the symptoms. Finally, however, as he happened to be palpating the middle part of the abdomen, the patient suddenly exclaimed: "That is the spot at which the pain begins." The removal of the offending omental protrusion, which was of no greater size than a large pea, completely cured the long-existing indigestion.

The second case reported by Bennett is also well worth reciting:

It is that of a man in whom there was discovered, about an inch above the umbilicus, a small, rounded, movable nodule, the size of a cherry. The patient had suffered for a long time from "intense rolling and cramp-like pains about the middle of the abdomen, which always followed the taking of food." He had been treated for dyspepsia, and all sorts of drugs had been prescribed without relief of symptoms. Operation disclosed a rounded nodule of fat (a congenital lipoma) which, terminating in a thin stalk, was continuous with the subperitoneal fat and passed through a small opening in the abdominal aponeuroses not larger than a No. 8 English catheter. The special interest in the case is in the fact, as narrated by Bennett, that it demonstrated conclusively that pains and discomfort indistinguishable from those

produced by an omental hernia in this situation may be caused by protrusion of a mass of extraperitoneal fat.

Lindner,[9] in a monograph on abdominal hernia, relates cases similar to the foregoing of previously unrecognized epigastric hernia in the linea alba.

In one, an army officer, the symptoms had existed for seven years, the hernia having probably been originated from a strain during violent exercise. His attendant then noted resistance in the epigastrium, and an ointment was prescribed. The patient continued to have violent epigastric pain, in one attack of which he fainted; in another there was considerable rise of temperature. He was often incapacitated, and consulted many physicians, all of whom diagnosticated gastric ulcer. The symptoms continuing, he went from one physician to another; was put on various diets and bath cures, and had frequent lavage; for a year before consulting Lindner he had been given daily massage of the epigastrium under the most violent pain, with an idea of the amelioration. He grew progressively worse, and at the expiration of seven years after the onset of symptoms he consulted Lindner, who found a small hernia in the linea alba, located "a hand's breadth above the umbilicus." Operation resulted in absolute cure.

Kuttner, an assistant of Ewald in Berlin, in an instructive paper[10] on "Digestive Disturbances Caused by Various Forms of Hernia, Especially Those of the Linea Alba," refers to the cases of Lindner and others, and cites the following very interesting instance of previously unrecognized, small, supraumbilical hernia, which had been productive of various ill symptoms:

A merchant, aged fifty-six years, for two years had had paroxysmal attacks of colic. Pain radiated from the epigastrium to the back, girdle-like; commonly one to two hours after food, especially after solid food; colicky pain on exertion, and especially on bending or lifting, ameliorated on assuming the recumbent posture. Lately gastric pain had been constant; no vomiting; bowels sluggish; tense abdomen, due to meteorism. Headache, vertigo and hypochondriasis were present. No tumor was ever noted by his physicians. Various forms of diet were tried. He was sent to a stomach specialist; normal gastric chemism found. Diagnosis: Nervous indigestion. Treatment accordingly; no benefit. As he had had lues twenty years before, inunction cure for syphilis was tried unavailingly. He was finally seen by Kuttner. A small hernia the size of a lentil was discovered in the linea alba, two fingers' breadth above the umbilicus, irreducible and very sensitive to touch. Operation resulted in restoration to health.

Kuttner remarks that these cases might readily be mistaken for various abdominal disorders, and especially for simple gastralgia

and enteralgia, for gastric ulcer and carcinoma, for cholelithiasis, and for gastric neurasthenia and hypochondriasis.

Although I have long had in mind the importance of this subject, I was, until I began this report, unaware of the extent of the literature on epigastric hernia, and held with Davis that its dearth was ample reason for non-recognition of these cases, showing direct and reflected gastrointestinal symptoms. Davis remarks that "the leading American text-books on surgery do not mention it at all or dismiss it with a line. Careful searches through a large number of American surgical works have failed to discover a word to indicate the severe gastric symptoms which a slight hernia in the linea alba may cause." This fact probably accounts for the paucity of knowledge on the subject shown by surgeons[11] and clinicians in this country. Abroad it has somewhat received the attention it merits, but not at all generally, either by clinicians or surgeons. Doubtless, nowhere is it commonly recognized that even a very small hernia in the linea alba may be the source of obscure and distressing abdominal symptoms, nor is the importance of a search for these small hernias as a routine procedure in the examination of the patient very generally in the mind of the clinician.

This review is purposely sketchy. In the brief confines of the paper, of value clinically, especially to direct attention to these cases, no attempt has been made at completeness of study of the subject. Such cases as have been cited other than my own have been taken for illustration from a considerable number of others very similar in the literature. A quite complete bibliography to 1897 is given in the paper by Kuttner and in that of Lathrop. Since these a few other reports of cases have appeared, which are chronicled in the *Index Medicus*.

Bibliography.

1. Mémoires de l'Académie royale de chirurgie; mémoire sur plusièurs hernies singulières, 1743.
2. Berger, in Traité de chirurgie, 1895, noted 137 cases in 16,800; and Bohland, in Polyclinic in Bonn, 33 cases in 3420; Kuttner.
3. Warren Gould. International Text-book of Surgery, 1902, p. 510.
4. Loc. cit.
5. Quoted by Davis, Annals of Surgery, i, 1895.
6. Loc. cit.
7. Medical Record, 1897, 52.
8. The Lancet, September 15, 1894.
9. Berliner klinik, 1892, Heft 49.
10. Mittheilungen aus den Greuzebieten der Medizin und der Chirurgie—Erster Band, 1896.
11. Warren and Gould (International Text-book of Surgery, 1892) state that "far too little prominence is given to this variety of hernia in the text-books on surgery."

CONCERNING THE OBSCURITY OF DIAGNOSIS SOMETIMES ATTENDING STONE IN THE KIDNEY; WITH REPORT OF CASES.

By D. D. STEWART, M.D.,[1]
OF PHILADELPHIA.

The presence of stone in the kidney is commonly apt to be regarded as fairly easy of determination when it exists in other than a quiescent state, and is suggested by the usual direct symptoms—the occurrence of loin pain, paroxysmal or continuous, with exacerbations aggravated by exertion, shooting into the groin, testicle, and thigh, and with the presence of blood in the urine. It is, however, well understood that various other morbid conditions of the kidney—the presence of a neoplasm; slight or, again, easily ascertainable displacement of the organ, causing torsion of the ureter; intermittent hydronephrosis, so produced or induced by a ureteritis; so-called "nephralgia," and the like—all simulate stone, and may cause its presence to be suspected when non-existing. Eshner[2] recently in reporting a case, the symptoms of which simulated stone, has painstakingly collected from the medical literature a rather extensive series of cases in which, with unilateral renal hematuria as the chief objective symptoms, stone, although suspected in a number, was later regarded as present in none.[3]

With symptoms suggesting stone, the diagnosis is now materially helped by the Roentgen ray, and yet both its positive and its negative finding may be misleading and sometimes mischievous; not least as concerns the latter is the fact that with too blind dependence

[1] Dr. D. D. Stewart died June 13, 1905.

[2] Unilateral Renal Hematuria, American Journal of the Medical Sciences, April, 1903.

[3] Although it should be said that the technic of the operative procedure for the recognition of stone was not always above reproach.

on its reading an abnormality other than stone, requiring surgical interference, existing, may escape consideration, and the ailment be regarded as a "nephralgia," although actually due to a condition only amenable to operation, such, for instance, as torsion of the ureter, the result of a slight or greater degree of mobility of the kidney, to a ureteritis, thus or otherwise produced, or to a kidney the functions of which are hampered by adhesions, as in one of the cases I report.[1]

It is said that renal calculus may rarely exist for a long time symptomless. The condition of absolutely quiescent renal calculus the writer doubts, and regards such cases as those not carefully studied as concerns past history and the urinary condition.

Presumed affections of other organs may be masqueraded by renal calculus, the symptoms of stone being so referred; contrariwise, gastric ulcer, gallstones, abdominal tumors, and affections of the bladder and ovaries may simulate calculus. It is only recently that the frequency of the occurrence of loose kidney causing symp-

[1] In the hands of a few experts the *x*-ray has proved of much service in the diagnosis of renal and ureteral stone, but even with these its negative finding cannot always be depended upon. The point of vital importance in its use seems to lie in the axiom which I think was first propounded by Leonard, that "where shadows of tissue less dense than the least dense calculus are shown in the skiagraph no calculus can escape detection." In other words, tissue differentiation must be apparent." Cole's rule (April 22, 1905, p. 761, cited by Brewer, Medical News) is an amplification of this, "that a diagnosis is not positive unless the outline of the psoas and the transverse processes of the lumbar vertebræ are distinctly visible in the radiogram, and, further, that the edge of the shadow of supposed stone be closely and clearly defined." Unfortunately there are few, even among those regarding themselves as competent radiographers, who, if alive to this vital rule, exemplify it in their work, whence arise errors.

It may be all very well to dilate on clear definition of stone and differentiation of the psoas, and to remark, as does a recent writer (Dr. Bevan, Medical News, April 30, 1905), that the *x*-ray has absolutely no fallacies, but it remains true, as Dr. Bevan also states, that "most of the work done with the *x*-ray in kidney stone has been poor work." Skiagraphers especially skilled in this field are not numerous, and even these are unprepared to admit absence of error. Leonard's statistics, which are remarkable when compared with the work generally done, show a failure to find but four calculi in 103 cases, out of a total of 331 suspects examined. His total errors in this number to the present are ten. One of the cases in which Dr. Leonard failed to discover a stone is the first of these related in this paper. In this case the stone was composed largely of calcium oxalate and was of fair size, and the anteroposterior diameter of the patient was not great. Two examinations were made at first by Dr. Sweet, and again two at my request by Dr. Leonard. The latter was positive no stone existed, until it later was removed by Dr. Keen. This, however, was over five years ago, but at that time Dr. Leonard had already realized the importance of differentiation of shadows less dense than the least dense stone; improvement in technic has doubtless occurred since. It is often difficult to interpret the *x*-ray plates in cases of suspected calculus, and not infrequently positive diagnoses err. Thus, periureteral bodies of different origin, such as a calcified tip of an appendix epiploica, have positively indicated ureteral stone (Brewer, Medical News, April 22, 1905, p. 761), and Caldwell also points out that renal and ureteral stones have been masqueraded by pseudoshadows in the radiograms of uncertain origin, and that these have deceived experienced *x*-ray operators.

toms—*i. e.*, intermittent torsion of the ureter, with moderate hydronephrosis—has received the attention it should as a cause of loin and abdominal pain. In this connection the writer has in mind a case seen a few years since with Dr. Lewis Brinton, in which, because of recurring attacks of severe pain in the region of the loin and groin, the patient, a young woman, before she came into Dr. Brinton's hands had been operated on for suspected appendicitis, and the appendix, presenting a healthy appearance, was not removed. The ovary, although equally healthy, was, since no other source for the ailment could be imagined. On recovery from the celiotomy the pain recurred as before. The surgeon now by the process of exclusion regarded his earlier diagnosis as correct and urged a second operation for appendectomy. The patient was now brought to me by Dr. Brinton; a loose, large, and painful right kidney was demonstrated. The symptoms were clearly those of slight intermittent hydronephrosis. An immediate nephropexy was advised. This was performed by Dr. W. E. Ashton. The patient was immediately relieved of and has since remained free from all discomfort.

It has not been altogether unusual in my experience to see cases with affection of one kidney variously diagnosed as appendicitis and as gastrointestinal disease. I recall a Polyclinic Hospital case, seen with Dr. T. S. K. Morton a few years ago, in which appendicitis had been suspected, but in which there was a frank history obtainable of intermittent hydronephrosis, and in which the ureter could be palpated as a thickened cord—here an obstructive ureteritis had originated the symptoms, and the thickened ureter suggested an elongated diseased appendix. I have in mind another case sent me by a prominent surgeon as one of dyspepsia. The patient had various abdominal symptoms and the case had been under casual treatment by the surgeon and his assistant for months as gastric catarrh. The abdomen, in the hurry of work, had not been examined. The usual routine examination at the first visit disclosed a large and very loose right kidney, and a urine examination showed a pyelitis. Recovery followed a nephropexy. There are cases other than stone in the kidney in which calculus was not suspected, but in which a distinct kidney abnormality often associated with stone had been

referred to another organ, and a too casual examination had at first caused error in diagnosis. They are referred to as in line with remarks that follow as to diagnosis of some special aspects of renal calculus and of kidney conditions simulating stone.

The purpose of this paper is not to discuss the general subject of diagnosis of renal calculus, but to report a small group of cases—cases with calculus and without it, though simulating stone, which, different in character, present features of such interest as to render their detail worth while from the standpoint of diagnosis.

Two of these were cases of unsuspected calculus, and one at least "masked" calculus, in neither of which had the diagnosis been made until seen by the writer. These, as well as Case III., the exact nature of which is still in doubt, were cases in which the symptoms had not been regarded as suggestive of an affection of the kidney. In the first of these (renal stone) there were absolutely no direct symptoms In the others, as in Case IV., they were only developed by careful inquiry, and the probable diagnosis in each could only be made by exclusion and by a study of the urine. One of these cases of stone had been in the hands of a surgeon of wide experience for months, and was treated as a case of dyspepsia before he was referred to the writer.

In another case which, with symptoms also not directly referable to the kidney, had been previously diagnosed as one of neurasthenic gastralgia, I had suspected stone in the kidney, but an exploration of that organ by Dr. Keen indicated dense adhesions and ureteritis as the cause of the pain. In another, the history of which precedes the foregoing, from the first, stone had been diagnosed, frank renal colic with recurring hematuria occurring, a strictured ureter without stone was found. In another with symptoms strongly suggestive of stone, in which explorations of the kidney had been performed by Dr. Halsted, the presence of calculus was still suspected by the latter and similarly by myself; later developments demonstrated the case to be one of pure hysteria, the renal colic apparently having been a mere expression of this condition. Doubt was felt for a long time as to the correctness of diagnosis, because of the deception practised by the patient. It is especially desired to emphasize the fact that renal calculus and allied conditions of the kidney will some-

times produce symptoms which express themselves chiefly or alone as a disturbance in the intestinal tract and that such cases may be overlooked unless repeated examination of the urine be made. Attention must be called particularly to the first case to be related, in which the ailment would have been regarded as a colitis but for the result of a study of the urine; also to that of the case which follows this, in which the suspicion of kidney stone, when the patient was first seen, was converted into a strong probability, on an examination, of a specimen of urine voided during the initial visit, showing the presence of considerable (microscopic) blood. In the case of C. M., referred to me as one of presumed bowel trouble, it was only after several visits that a specimen of urine was obtained; then the presence microscopically of considerable erythrocytes and their persistence in each specimen examined subsequently, with absence of urethral or bladder disease, caused me to suspect stone. Here so unusual was the absence of direct symptoms that operative interference was refused by a surgeon to whose hospital service I at first sent him. The history of the case is as follows:

Case I.—C. M., aged twenty-three years; weaver. Referred to me by Dr. R. H. McCamy on October 15, 1898. Symptoms of bowel disorder. The history then elicited was: He had developed chronic diarrhea when about seven years of age, which had lasted some six years. There had been a good deal of abdominal pain with this, from which afterward he had never been entirely free. When he consulted me there were soreness and pain extending across the abdomen in the direction of the transverse colon, to the extent of several inches, and thence downward for a short distance following in the line of the descending colon and sigmoid. Here at one point (see diagram), two and one-half inches below and one and one-half inches to the left of the umbilicus, there was marked tenderness on pressure, and about this area colicky pains would occur. With this pain, and apparently aggravating it, there was a good deal of flatulent distention of the colon. Physical examination disclosed a myasthenic, dropped stomach, in which a very audible splash sound was present five hours after food and drink. Marked distention of the bowel and rigidity of the abdominal wall prevented the left kidney from being readily palpable. On two occasions its lower pole

was detected, but sensitiveness could never be elicited by manipulation of the left loin.

The symptoms suggested a colitis, and only the usual routine examination of the urine prevented this mistake being made. The urine was clear; of amber color; specific gravity 1020; deposited but a light flocculent sediment after some hours' standing. A fair trace of albumin (heat and acetic acid) was present, and microscopically an uncentrifuged specimen showed many leukocytes and a few red blood corpuscles, with a moderate number of hyaline casts and cylindroids.

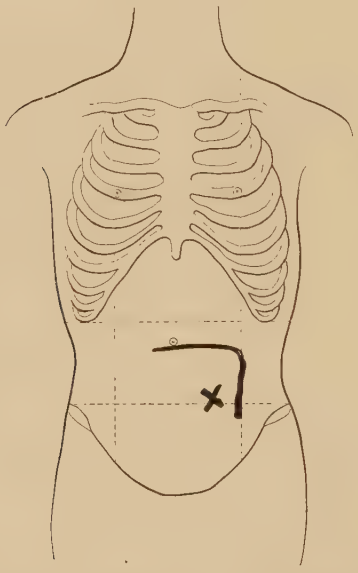
Further questioning now elicited the history of a strained back, through very heavy lifting, four years before. About a year following there was a good deal of pain in the dorsal region and in the left side. This afterward disappeared, and the only pain he had had lately was that before mentioned in the region of the transverse and descending colon. There was no history of gonorrhea or of past or present bladder trouble. The patient was now seen a half-dozen times at intervals of one to two weeks. During this time careful study of the urine was made both by Dr. Ghriskey and myself. There were always present a fair trace of albumin, many erythrocytes and pus corpuscles, hyaline casts, cylindroids, and streptococci. Occasionally cells, presumably from the renal pelvis and from the ureter, were found. Coincident with marked aggravation in attacks of abdominal pain, toward the end of December, red blood corpuscles and pus cells were present in the urine in much increased number, but the blood or pus never was evident macroscopically. The urine was always of acid reaction, of normal color, specific gravity 1017 to 1020, 1000 c.c. in twenty-four hours, and never contained more than traces of free uric acid crystals. Calcium oxalate crystals were never seen. Tubercle bacilli were examined for on a number of occasions resultlessly. Marked variation in the amount of urine voided from day to day was carefully watched for for some time, but did not occur. The patient had never had urethral or bladder disease.

The pain had become more paroxysmal, especially when about and at work, yet would often appear before rising in the morning, and at times was very severe; there never occurred any indication of

renal colic, or of radiation of pain into bladder, testicle, or thigh. The pain followed the path before described from the umbilicus, across and thence downward for two to three inches in the line of the descending colon, and was at first thought to suggest a colitis. It was associated with flatulent distention of the bowels and was relieved by the expulsion of gas.

I regarded the case as either slight ureteral stricture from a preceding ureteritis, the result of past injury to the kidney, the result

FIG. 1

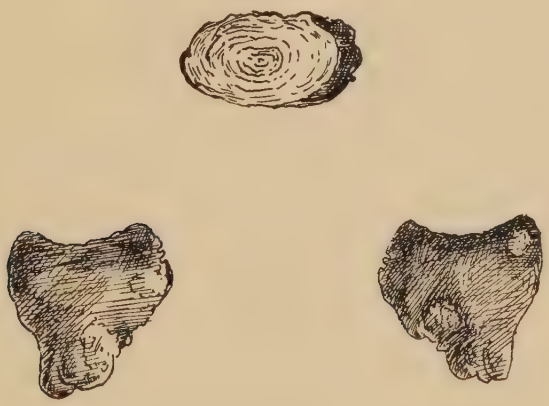


The cross marks the situation of crampy pain and of sensitiveness; the right angle the situation of persistent soreness, suggesting colitis.

of traumatism (strain), or one of renal calculus. The man was a poor weaver, with a family dependent upon him, and was most adverse to abandoning work for the purpose of exploratory operation. His consent was finally obtained in January, three months after he first came under observation, at a time when he was temporarily out of employment. I then referred him, for exploration of the kidney, to the surgical ward in one of our hospitals. Unfortunately, the surgeon on duty, after an examination of the case, and detaining him

for some little time in the wards for observation, refused operative interference, not regarding the symptoms as suggestive of a kidney or ureteral ailment. This rendered the patient thoroughly averse to surgical interference, and it was not until some months later, when I began my service in the Episcopal Hospital, that I could do anything further with him. I then had him admitted, for exploration of the kidney, to Dr. T. R. Neilson's ward. A skiagraph taken by Mr. Riegel indicated the presence of a rather large calculus in the left kidney, which the operation by Drs. Neilson and H. C. Deaver disclosed.

FIG. 2



Exact size of stone.

The stone, of triangular shape, lay in the pelvis of the kidney; one end, shaped like a pig's snout, engaged the mouth of the ureter. The kidney was somewhat enlarged and placed a trifle lower than the normal. The stone was of good size when freshly extracted, weighing eighty grains. It was made up in very nearly equal amounts of uric acid and of calcium oxalate.

The accompanying sketch, made by my friend Dr. J. Madison Taylor, shows the exact size of the stone. For a description and very complete analysis of the stone I am indebted to Prof. H. F. Harris, formerly of the Jefferson Medical College. In concluding his report Dr. Harris remarks:

"From the various reactions given by the substance composing

this calculus it appears certain that the nucleus is made up in very nearly equal amounts of uric acid and calcium oxalate, and that the outer portions are composed almost entirely of calcium oxalate, with a small amount of organic coloring matter and probably slight traces of other organic substances."

It is of interest that the following case of stone in the kidney had, prior to coming under observation, been treated for some months as one of dyspepsia by a surgeon of recognized skill. In the rush of a busy practice time had not been taken for thorough examination, and the presence of intestinal indigestion with marked aggravation of symptoms through dietetic errors misled.

Case II.—W. H. K., aged thirty-six years; bookkeeper. Referred to me on December 1, 1899, by Dr. H. F. Hansell. The patient had had for over eighteen months pain in the abdomen, which had been diagnosed and treated by a half-dozen general practitioners and lately by a surgeon as gastrointestinal disorder. The pain was more or less continuous and of moderate severity, but with paroxysmal aggravation so severe as to "double him up." These paroxysms were usually of very sudden onset, striking him, as he described it, "like a shot." He would be practically free from pain, and then, without physical effort on his part, pain would appear, and become of great severity. Pressure applied to the loin and abdomen by the hand commonly greatly relieved the pain. Such pressure he applied when walking about, and frequently at night on retiring. For a long time he had been unable to lie on the right side, because of a paroxysm being thus immediately induced. He could lie with moderate ease on the back. Walking about often relieved the lighter paroxysm, and pressure by the hand sunk into the loin and upward against the ribs would also give him relief. His digestion had not been good for a long time, and a slight dietetic error would invariably aggravate the pain. There was a great deal of bowel flatulency, but passage of gas was difficult. After the expulsion of flatus the pain would commonly be lessened. The pain never radiated toward the groin or into the loin.

Eating or drinking anything cold tended to induce a seizure. Although of fairly robust appearance, he had lost twenty-five pounds in the past year. The skin was of an unwholesome, bronze hue.

His appetite was slight, and the digestion greatly impaired since the ailment first appeared.

Fig. 3

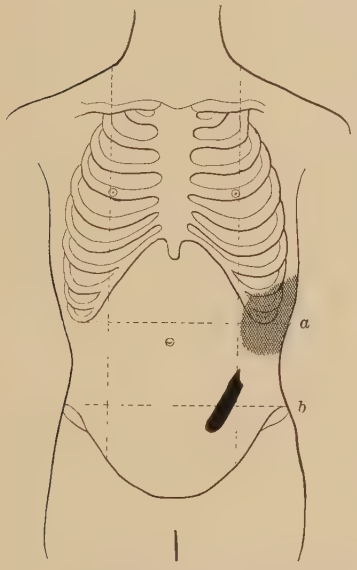


Fig. 4

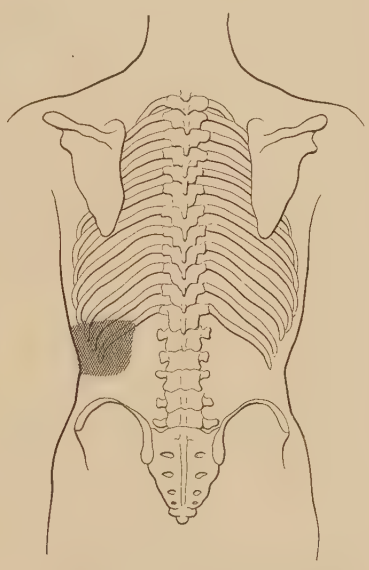


Fig. 3.—Anterior area of pain : *a*, area of pain ; *b*, very sensitive to pressure. Shooting pains in this area, but never to groin or kidney.

Fig. 4.—Posterior area of pain.

Blood had never been noted in the urine by the patient, and he had at no time remarked frequency of urination or symptoms sug-

Fig. 5

gesting ureteral obstruction. His symptoms, as narrated, were to me so strongly suggestive of renal calculus that I told him, before I examined him, that I thought this the probable diagnosis. Exam-

ination disclosed decided tenderness in the left loin, more marked posteriorly and anteriorly in the situation noted in the diagram. Along the middle part of the course of the ureter, in the region of the sigmoid flexure, palpation was very painful. The left kidney was deeply and so highly placed that on the fullest expiration, with the abdomen relaxed, its lower pole could only be made out by bimanual manipulation.

The freshly voided urine, examined at the time of his first visit, showed an abundance of red blood corpuscles, singly and in large groups, and a small amount of free uric acid crystals. The specimen was of high acidity. There was a decided trace of albumin. The result of a number of examinations subsequently made both by Dr. Ghriskey and myself before operation were similar to the above.

The *x*-ray examinations were made at my request by Dr. Sweet at the Jefferson Medical College, and two by Dr. Leonard at the University. As a result, both gentlemen gave the positive opinion that no stone existed. I referred the patient to Dr. Keen for exploratory operation, suggesting that the diagnosis lay between stone in the kidney and strictured ureter, renal calculus being the more probable, despite the lack of *x*-ray confirmation.

Operation by Dr. W. W. Keen on January 6th. The kidney was very firmly adherent and placed somewhat higher than usual. It was enlarged and deeply congested. A stone was removed from the pelvis. It was 12 x 10 x 5 mm. in measurement. An analysis made by Dr. W. M. L. Coplin showed that it was composed almost solely of calcium oxalate.[1]

The patient made a rapid and uninterrupted recovery, even while abed, two weeks after the operation, taking and digesting with ease food that previously he had not been able to eat for nearly two years.

A case strongly suggesting the preceding one is now under observation, and is worthy of brief narration:

Case III.—H. M., aged fifty-five years; merchant; first seen March 22, 1905. Consulted me on account of "indigestion" and

[1] I am indebted to Prof. Coplin for the accompanying photograph and for a very complete report of his analysis of the stone.

"uric acid in the system." For two or more years past he has had attacks, usually at night, of severe pain in the lower part of the abdomen, limited chiefly to the left side. The pain is associated with marked flatulent distention of the abdomen, "rumbling and rolling in bowels," and he thinks is so initiated. Expulsion of gas by bowel relieves the pain, but he is generally unable during an attack to pass flatus. Although not constipated, purging with salts assuages the pain. Rising from bed and walking about enables him to better expel flatus and thus tends to assuage the pain, but if the latter is severe a chill is apt to occur on getting up. There is only occasionally a tendency to frequent urination during the attacks. No alteration in color of urine observed and no gravel passed. No nausea or vomiting during a seizure. Appetite good; careless as to diet; rapid eater; teeth in good condition. No symptoms of stomach disorder. Much confined in-doors. Five to seven cigars daily; no alcohol; no lues. La grippe only ailment has ever had. No loss of weight.

Physical Examination. Color of skin normal. Rather high blood pressure; radials trifle thickened; no cardiac hypertrophy or valvular lesion; accentuated second sound at apex.

Abdomen much distended with gas, chiefly intestines; stomach undilated; umbilical hernia. Marked sensitive point always present two inches below and two and one-half inches to the left of the umbilicus—in the situation noted in the case of C. M. No sensitiveness or pain elsewhere in first examination. Examination of stomach contents showed normal secretory activity; delayed motility. Urine voided in laboratory: clear, light amber; acid; specific gravity 1011; albumin plus normal trace, microscope; no centrifuge used; cylindroids; uric acid crystals; leukocytes; few red blood corpuscles.

Provisional Diagnosis. Arteriosclerosis; abdominal pain on expression of the arteriosclerosis, or due to intestinal indigestion.

Treatment. Diet regulated; fresh air; no tobacco; blue mass, followed by Glauber salt; morning dose of Carlsbad subsequently; tincture nux vomica and nitroglycerin. At bedtime betanaphthol, 5 grains in tincture of ginger 1 drachm.

No improvement on the above. Pain occurred as before; stone in the kidney suspected. Naphthol discontinued; daily examination

of urine made; all specimens (centrifuged) show red blood corpuscles, singly and in groups, with a fair number (about one-third in proportion to red blood corpuscles) of leukocytes; hyaline casts in small number in most specimens; polyhedral cells, presumably from tubules, similar to those making up two epithelial casts seen; few caudate cells, presumably from renal pelvis; uric acid crystals.

Severe attack of pain in left loin, night of April 4th, with tendency to shoot toward pubes and into the inner side of thigh. Sensitiveness in the left loin laterally and posteriorly the morning after, and in the abdomen to the left and below the umbilicus. Urine voided (11 A.M.): amber, acid; specific gravity 1022; slightly plus normal trace albumin; centrifuged twenty-five minutes; red blood corpuscles scattered in all fields, from two to three to eight to fifteen; many fields contained over a dozen; a few groups of from four to twelve, with a fair number singly; leukocytes in moderate number; stray cylindroids and hyaline casts; few granular cells, twice the size of polymorphonuclear leukocytes. *x*-rayed twice by Dr. Leonard. Negative.

Now for a few days no severe attacks occurred. At the present writing (April 20th) pain has returned as before, and marked sensitiveness exists anteriorly from the loin to the pubes, but especially along the middle course of the ureter. The pain as described has occurred from just below the false ribs to the pubes. Loin sensitiveness to pressure in this examination, but not so markedly as in the middle situation of the ureter.

This case is regarded as either one of renal stone or as ureteritis. There are no indications of tuberculosis or of renal neoplasm. It resembles in character that of the two preceding.

There is a rather extensive anteroposterior diameter of the abdomen. Leonard was unable to outline the kidney in the skiagraph, but from his negative finding regards stone absent. An exploration of the kidney is under consideration.

A case resembling the foregoing is the following: In this case the diagnosis lay between stone in left kidney or presence of a neoplasm. The patient was lost sight of after twelve days' observation.

CASE IV.—L. J. F., aged sixty-three years; clerk; first seen June 16, 1902. Referred to me by a colleague for presumed gastrointes-

tinal disorder. For four or five years he had had a good deal of distress in the abdomen, in the region of the descending colon, which for the past few months had been greatly aggravated, and for a few weeks it had practically incapacitated him. Continued soreness, with attacks of severe colicky pain, lasting from a few hours to two or three days; pain usually starts with a griping sensation in the region of the sigmoid and ascends to the loin, but is not felt laterally or posteriorly. It may be so severe that unless relieved he has a sensation of impending death during the seizures. The passage of flatus promptly relieves him, as does, too, but to a less extent, the application of heat; no frequency of urination; bowels much constipated. Eight years before passed a tape-worm, after extended and futile treatment. Then had pain in region of the sigmoid for a long time.

Physical Examination. Thick-walled abdomen; sensitiveness along region of descending colon and laterally in the loin, but not in the loin posteriorly; impaction of feces; arteriosclerosis; heart normal; accentuated second aortic sound at apex.

Examination of stomach contents shows high-grade hyperchlorhydria; large high enema and castor oil by the mouth ordered. An enormous quantity of hardened feces passed. Obstruction of the colon by neoplasm or simple stricture was thought of in the first examination. However, 1500 c.c. of fluid was readily passed into the bowel without pain or distress after it was first emptied and subsequently the bowel was inflated without discomfort. Colon and sigmoid tympanitic; no abnormality detectable; despite thorough evacuation of the bowels attacks of pain occurred as before, and sensitiveness in the loin laterally, but not posteriorly, noted. Pain shoots into the left testicle.

Urine Examination June 16th. Acid; amber; specific gravity 1018; well-marked trace of albumin. Microscopically: all fields crowded with red blood corpuscles; numerous leukocytes. Centrifuged specimen showed blood sediment. Specimen June 28th, voided in laboratory: clear, light amber; acid; no visible sediment; albumin, moderate trace. Centrifuged specimen: all fields crowded with red blood corpuscles; few narrow hyaline casts; granular debris; stray leukocytes. On careful inquiry fact elicited that five

weeks prior to his first visit urine on one occasion was noted to be very dark, presumably bloody.

The patient was unwilling to undergo the expense of an *x*-ray examination by a competent man, and would have refused operation if stone had been thus detected. He was under observation only twelve days. Since then I have been unable to locate him.

Of these 4 cases, operation disclosed stone in 2, as was previously diagnosed. In the 2 last described there is little doubt that the symptoms also had seat in the left kidney or ureter, but whether the disorder be stone, a ureteritis or a renal neoplasm it is now impossible to determine. It is of especial interest that in all these cases the symptoms were more or less referred from the offending organ to the bowel. In but 1 of the 3 did I suspect stone in the initial visit. In the first of these cases described I was originally completely deceived as to the nature of the ailment, and only examination of the urine suggested it. In Case III. several visits were made before the likelihood of the kidney being the seat of the trouble occurred to me. In Case IV., also, it was only after attention to the bowels, excluding disease here, that the notion of stone or another gross kidney lesion was considered. It is especially interesting that without examination of the urine in the first of these cases of stone the correct diagnosis would not only have been impossible, but would probably not have even suggested itself.

I wish especially to call attention to the chief location of pain in three of the cases, which was also manifest, though to a less degree, in the fourth (Case II., in which stone was diagnosed and removed), an area of extreme sensitiveness to touch and of unprovoked pain below and to the left of the umbilicus, at about the site at which the ureter crosses the pelvic loin. I have nowhere seen this symptom noted, and my experience in these, and in other cases of stone with frank symptoms, suggest it may be of value in diagnosis.

In Case II., in which the influence of posture on the pain was very marked, and in which, as in Case III., the pains were pronouncedly aggravated at night in recumbency, the pain was referred anteriorly along a portion of the ureter covered by the sigmoid flexure (see diagram, Case II.). The diagnosis in this case was the least difficult. At the initial visit, after eliciting the history, and

before making a physical examination, I suspected stone, and so informed the patient. Here the unvariable aggravation of symptoms through a dietetic error, which coincidently induced bowel flatulence, and the marked relief in pain after the passage of gas, totally misled his former attendants.

Of these cases, as remarked, operation disclosed two to be renal calculus. The second two, unoperated on, may be here grouped with them, as, if not those of stone, at least due to a unilateral renal abnormality simulating it. The surface symptoms of all were outside and away from the kidney, thus placing them in the category of so-called "masked" calculus. Whether two of these be stone is less material than that a study of the cases at least made clear the location of the ailment in the kidney previously regarded as having seat in the intestines.

A condition termed arteriosclerotic abdominal pain has lately attracted considerable attention, and there is now on record a number of these cases[1] in which, as described by Buch, as a result of a sclerosis of the vessels in the splanchnic area, the chief symptom is recurring abdominal pain. The pain is paroxysmal, of frequent recurrence, and is induced by the factors exciting anginal seizures, with which it is in no one group associated. The pains have their seat almost always above the umbilicus, and are only exceptionally associated with digestive disturbance or meteorism. It is with such cases that the second two of the above reported might be confused, since in these, with attending renal fibrosis, the frequent presence of red blood cells in the urine could not be regarded as unlikely. The first of these cases (H. M.) in the initial examination, with no cause for pain evident, I was inclined to place in this group. The ages of each, fifty-five and sixty-three years, and the presence of indications of general arteriosclerosis were in its favor. But the invariable one-sidedness of the pain, its situation below the umbilicus and the presence of distinct digestive (bowel) disturbance with combined marked meteorism, plus the indications of unilateral renal disorder, opposed this view.

It should be remarked that in the diagnosis of renal calculus no

[1] Max Buch. St. Petersburger med. Wochen., 1904, vol. xxvii., has recently collected and analyzed 25 cases from literature and from his own observation.

stress is laid on the mere presence of microscopic blood in the urine, without other discoverable symptoms of unilateral kidney disease, since it is not unusual for red blood corpuscles to be more or less constantly found in cases of chronic nephritis, even with the scant presence of casts, and their occurrence through tubule irritation in oxaluria and lithuria is well recognized. It is their more or less persistent presence with symptoms which may be intelligently interpreted to indicate unilateral kidney affections, whether stone or a lesion of another sort, that is significant in this particular, as it was in the four cases just detailed.

Frank renal hemorrhage, in cases in which both the symptoms and a cystoscopic and ureteral examination show to be unilateral, may occur without the presence of calculus, as it may without apparent evidence of a gross anatomic alteration in the kidney. In Eshner's[1] review of the literature of unilateral renal hemorrhage he cites several interesting instances, and more recently H. Schüller,[2] in a "Contribution to the Study of Hemorrhage from Apparently Normal Kidneys," reports a case of recurring and obstinate "unaccountable renal hemorrhage," shown to proceed from the right kidney, in which, by exploration and the usual autopsy incision, no gross lesion was found, but in which an examination of a bit excised showed evidence of an old inflammatory process. In a review of the literature of unconcealed unilateral renal hemorrhage, in cases in which gross lesions were regarded as absent, he finds two which were not evidently pathologic, and these he prefers to class as "unexplained," rather than to permit such to be described as hematuria without lesion, "local hemophilia" (Senator), "essential hematuria,"[3] or "angioneurotic hematuria" (Klemperer), "hemorrhage from healthy kidneys."[4] The various pathologic findings in these cases he groups as congenital malformations, diffuse unilateral nephritis, glomerulonephritis, fibroid degeneration of the fatty capsule, mechanic lesions and their effects, and a growth including such a case as Abbé[5] described, in which the hemorrhage apparently arose from a calcareous incrustation of a papilla.

[1] Loc. cit.
[2] Wien. klin. Woch., 1904, Bd. xvii. p. 477.
[3] Nitze. Vereins-beilage der Deutschen med. Woch., February 18, 1897, p. 54.
[4] Deutsche med. Woch., February 25, 1897.
[5] Medical Record, May 16, 1891.

He holds that in cases not so included careful examination should practically always reveal some organic lesion, however insignificant.

But the likelihood of the existence of undiscovered stone in certain of these cases is not sufficiently excluded. It has only in the past few years begun to be generally understood that by mere exposure and palpation (in Eshner's case of unexplained unilateral hematuria the kidney was exposed and manipulated, but not explored), and even repeated needling[1] without section, stone cannot be excluded, and the likelihood of a calculus of small size being overlooked by the usual incision of the kidney and exploration of its pelvis been apparent. This difficulty is well illustrated in a case reported by Abbé,[2] in which, but for the previous unmistakable findings, a presumed thorough search for a calculus in an incision made through the greater curvature of the kidney into the pelvis would have been finally abandoned as resultless, and the case classed as one of simple pyelonephrosis. Similar cases in the past few years have come to my notice. A study of paraffin casts of the pelvis of the kidney and the relation of the pelvis to the calices, made in the laboratory of the Episcopal Hospital some years ago by Dr. Ghriskey, graphically showed the irregular branching of the latter, and explained the difficulty often encountered in finding even an unencysted small stone. It demonstrated to us the necessity for a section of the kidney of sufficient size that all parts of the pelvis may be explored, and by a route to the kidney which also permits of ready access to the ureter.

I wish now to describe three cases of unusual interest, the symptoms of which suggested stone in the kidney, and in two of which the correct diagnosis was impossible without exploration of the kidney. In the first case to be related, which occurred before the advent of the Roentgen-ray method, there were certain of the usual symptoms of calculus, hematuria, both frank and larvated, with recurring attacks of renal colic. Death occurred from acute nephritis, complicating an attack of influenza, while the case was under observation. A necropsy revealed a strictured ureter, which, causing intermittent hydro-

[1] As is remarked by Morris, Renal Surgery, p. 118, "needling the kidney for diagnostic purposes is most unreliable and should be abandoned."

[2] Annals of Surgery, August, 1899, p. 186 *et seq.* Observations on the Detection of Small Renal Calculi by the Roentgen Ray.

nephrosis of small degree, with hematuria, originated the symptoms.

Ureteritis as a cause of simulation of renal calculus is of special interest. It is, as remarked by Morris, a disease which has attracted more attention in Germany and France than in England or the United States, and has been especially studied by Israel. Case II. of this series is probably also one of this sort, a ureteritis existing as a part of the general perinephritis found.

The occurrence of hematuria is especially interesting in the case to be described as a symptom of slight intermittent hydronephrosis due to ureteral obstruction. There are a few of these cases on record. Bangs,[1] in a search of the literature, was able to collect but 13 cases in which hydronephrosis was associated with hematuria.

Case V.—G. W. B., aged twenty-six years. First seen August 3, 1894. Patient was referred to me for examination by Dr. W. W. Keen, with a diagnosis of probable stone in the kidney. He had been in good health until five years before. He then, without noticeable premonitory symptoms, had an attack of severe pain in the right loin. It was of precipitated onset, and of about ten hours' duration. After a two months' interval of freedom, a second similar attack occurred, associated with profuse hematuria, and this seizure was followed by others without noticeable hematuria, at intervals of from four to six weeks for the first year, about three weeks' intervals during the second, and during the following three years had attacks with an interlapse of one to two weeks. In the year preceding they had been less frequent, not over six occurring at intervals of from one to three months. He had noticed it usual that, when occurring at about weekly intervals, the seizures were not so severe as when a longer period intervened. The onset of nearly all the attacks, save the first, was marked by the early occurrence of a dull aching in the loin, not existing previously, and accompanied by chilliness without a rise in temperature. The pain, increasing in severity, reached an acme in a few hours, and so continued for some hours, and then gradually declined, the dull ache or soreness com-

[1] Medical News, February 11, 1905.

monly remaining for two to three days. The fixed pain which occurred in the loin with the seizures was not felt laterally or anteriorly, and occasionally radiation along the ureter to the bladder was noticed; and in a seizure he had in a day or so after he first saw me there had been pain felt in the head of the penis. A moderate degree of bladder irritability during the attack was common. Vomiting was usual during the height of the seizure. The appearance of the urine, save on the occasion of the second attack, had not suggested to him that it contained blood; gravel in some amount he had occasionally noticed. He had never remarked increase in the amount of urine during the subsidence of an attack, nor diminution preceding, nor a sensation of fulness in the loin to suggest a hydronephrosis. No pain was present in the intervals, and no tenderness existed on manipulation of the loin in these examinations.

During the early period of the seizures the condition of the stomach seemed to influence their occurrence. Errors in diet would, he said, precipitate an attack. This relation he had not, however, noticed very lately.

The patient had seen several eminent medical consultants with Dr. Marcy, his attendant, but, despite the treatment, his ailment continued. He was referred to me by Dr. Keen, in order that a careful study of his case be made and a course of medical treatment instituted prior to resorting to operation, to which the patient was then absolutely opposed. The patient was noted to be of spare build; height, five feet six inches. His present weight was 113 pounds, a loss of about twelve pounds from his best five years before. His general health was fair, apart from the occurrence of these seizures. He had never sustained an injury or strain to the back or loin in any manner that he could recall. Physical examination of the abdomen revealed nothing abnormal, except that at bimanual palpation there was a somewhat increased resistance on the right side. There was no indication of tumor, nor was the kidney distinctly palpable. Tenderness was absent.

He had previously lived in a malarial district, but never had had chills or fever. Repeated blood examination showed no plasmodia. Several examinations of the urine in the intervals, and one during an attack, all showed red blood corpuscles in large numbers,

clumped and single; pus cells in moderate number; free uric acid in abundance (in freshly voided, centrifuged urine), and on one occasion only calcium oxalate. (This examination was made eighteen hours after voiding.) Casts were always present: hyaline, coarsely and finely granulated, broad and narrow, and, sparingly, epithelial casts; cylindroids always abounded. Albumin was present in moderate amount. Tubercle bacilli were carefully searched for over some time resultlessly. Specimens voided during and at the termination of a seizure were especially rich in red blood corpuscles and in pus cells. Twenty-four-hour specimens were collected over some time, to assist in determining whether there were sufficient variation to suggest obstruction of the ureter. But there was practically no variation over a considerable period, and a constant watch for indications of flush-tank symptoms was resultless.

Considering all the facts in the case, Dr. Keen and myself regarded the diagnosis of stone in the kidney as probable. The patient was given piperazin in doses of ½ drachm daily, which he took for about three months, alternating it at short intervals with lycetol in similar doses. Curiously, after a few weeks' trial of the remedy the attacks diminshed in severity, and were apparently not so readily induced by exertion as formerly, and he regarded himself as decidedly improved. With this view, however, I did not coincide, and repeatedly urged on him the necessity of an exploratory operation, as the presence of blood showed no material change, but his apparent improvement made him even more averse than at first to operation. During October and November he travelled a good deal, and was infrequently seen. On October 8, 1894, Dr. Marcy reported that he was very ill with influenza, complicated by acute nephritis; that his temperature had run very high, and that his urine, which at first was voided in full amount, contained much albumin and many casts. On the second day of the disease the urine was visibly bloody and became diminished in amount. The patient lived in another town, and I saw him but once after this with Dr. Marcy. Under active treatment improvement occurred, and secretion of the urine was re-established. On the seventh day of the disease, while apparently doing well, a severe rigor, followed by total suppression of the urine, occurred, and he went into a condition of collapse, during which

death occurred. His mind remained clear throughout the attack up to the time of his decease.

The postmortem examination made by Dr. Marcy was limited at the request of the family to the kidneys. The right kidney was enlarged and adherent to the adjacent parts. The ureter was strictured at a point two and a quarter inches from the pelvis. This constriction extended for an inch. An ordinary probe, No. 3 of the French catheter scale, would pass, but a probe of No. 8 size would not pass the obstruction (Dr. Keen). The renal pelvis and the ureter above the constriction were dilated; the pelvis contained from four to six ounces of bloody urine. The left kidney was also reported by Dr. Marcy to be much enlarged and to be "the seat of acute inflammatory change." The specimen was given to Dr. Coplin for pathologic examination, but, unfortunately, it was mislaid without other than the above observations of Dr. Keen and Dr. Marcy being recorded.

In the following case the diagnosis was in doubt for some time. The subject was highly neurotic. The symptoms were largely gastrointestinal. There were recurring attacks of obstinate and severe gastralgia and enteralgia. A careful study of the case caused me to place the diagnosis between stone in the kidney and ureteritis, but in favor of the former. Operation by Dr. Keen disclosed a kidney apparently healthy, so densely bound by adhesions that its delivery through the wound was impossible; it was likewise impossible to gain access to the ureter. The adhesions interfering, as they probably did, with the function of the kidney and the ureter, were doubtless the cause of the symptoms. The frequent presence of microscopic blood in the urine and the finding of streptococci suggested stone, probably associated with a (microscopic)[1] pyelitis.

Case VI.—C. H., aged thirty years; milk dealer. The history elicited was that he had been in good health until seven years before. Then a condition of mental and physical unrest developed, without assignable cause, and he "had to keep constantly on the go." About three years later he had a seizure of a curious character. He was nervously apprehensive on rising in the morning, and this continued

[1] Pus cells were always in less amount than were red blood corpuscles.

through the day; there appeared a sensation of numbness over the whole of the left half of the body, which remained for several days; with this, and also continuing for several days, there was a good deal of abdominal cramp. He was thus confined to the house a week. A second seizure of this sort did not occur until June, 1898 (three and a half years later). The third appeared again in two months; and since then the seizures occurred at intervals of two to four weeks, and lately about two weeks apart. Most of these later seizures were as follows: Crampy pain began a little above the umbilicus, and thence radiated over the abdomen; the pain was of greater intensity above than below the umbilicus, and more severe to the left than to the right. Colicky pain lasted steadily three to four days, and he was commonly housed a week by an attack. During a seizure the abdomen was rigid, but not especially distended by gas, nor tender on pressure. Pressure rather relieves the pain, as is usual in paroxysms of lead colic. The attacks necessitated a free use of morphin hypodermically. He had lost fifteen pounds in the past year or two.

Physical Examination at the Date of First Visit. Chest: Heart normal, first sound lacking in tone; lungs normal. Abdomen: Liver and spleen, outline normal; neither kidney plainly palpable; stomach slightly dropped. Fine tremor about the lips and in the tongue on protrusion; purplish line on gums; knee-jerks exaggerated; station and pupils normal; skin of sallow hue. Is an excessive tobacco chewer; habits otherwise good. No lues. No neurotic family history obtainable. No source of lead poisoning evident.

Later, the following was elicited: Attacks nearly always occurred between 10 P.M. and 2 A.M., but one recent seizure had occurred at 6 P.M., lasting two days. This came on before he had eaten supper, and while his wife was in the throes of confinement. It occurred while he was sitting talking with the nurse, and in no way previously nervous or excited. The pain came on gradually, reaching its acme in one and a half hours.

No symptoms of indigestion were prominent, and he has not noted (as in the case of K.) that a dietetic error precedes the attacks. The bowels were commonly constipated. Examination of the stomach contents showed practically normal secretory power and some

impairment of motility, with imperfect, starchy transformation. Blood examination for plasmodium, negative. Urine examination first made, negative.

The diagnosis by a process of exclusion was at first ordinary gastralgia in a neurotic subject. Treatment directed to improving the gastric myasthenia and the general physical and nervous tone was efficient. He gained in weight and improved in appearance, and the attacks were of less frequent occurrence. After a few weeks' treatment he passed for a time from observation. In July, four months after he was first seen, it was noted that in the attacks, which still occurred, pain began in the centre of the abdomen, at first slight, but soon augmented so in severity as to necessitate the use of morphin. Pain diffused from the centre of the abdomen to the left hypochondrium, and then into the back over the region of the left kidney, limiting itself at first to these two situations, and sometimes radiating toward the pubes, but finally diffusing over the whole abdomen, but lower and more intensely on the left than on the right side. He thought the urine was frequently scanty in amount during the seizure, but frequent desire to void the urine was not common. At this visit I began to suspect the likelihood of renal calculus, and then arranged for an *x*-ray examination. The specimen of urine then examined was negative; no albumin and no red blood corpuscles or leukocytes noted. On July 1st it was remarked that for the past few days he had had considerable pain in the left loin through the back, and that he had not been able to lie without discomfort on the left side. Urine examination again negative. *x*-ray examination by Dr. Leonard negative as to stone.

October 3d: my case-book notes four severe attacks since the preceding June, each of from three to five days' duration. In two of these the deep-seated, dull ache in the left loin developed as the pain anteriorly ceased; this continued for several days (three to four) and was of pronounced severity. To ease it he was compelled to lie during this time with a soft pillow under the loin. On another occasion pain occurred along the course of the lower part of the left ureter. In all the attacks pain was felt in the left hypochondrium, extending into the back.

On October 11th an attack occurred, the pain of which was

centred in the epigastrium above the umbilicus, and did not extend into the back or loin. On November 4th an attack of four days' duration, about forty-eight hours (severely) in the epigastrium and (lightly) for nearly the same period in the left loin. On January 9th, it was noted, no attack since the above, but constant slight or considerable distress in the left hypochondrium, with a sensation as if a heavy weight occupied this region. Urine then voided in laboratory showed scattered red blood corpuscles, and in two flakes a great

FIG. 6 FIG. 7

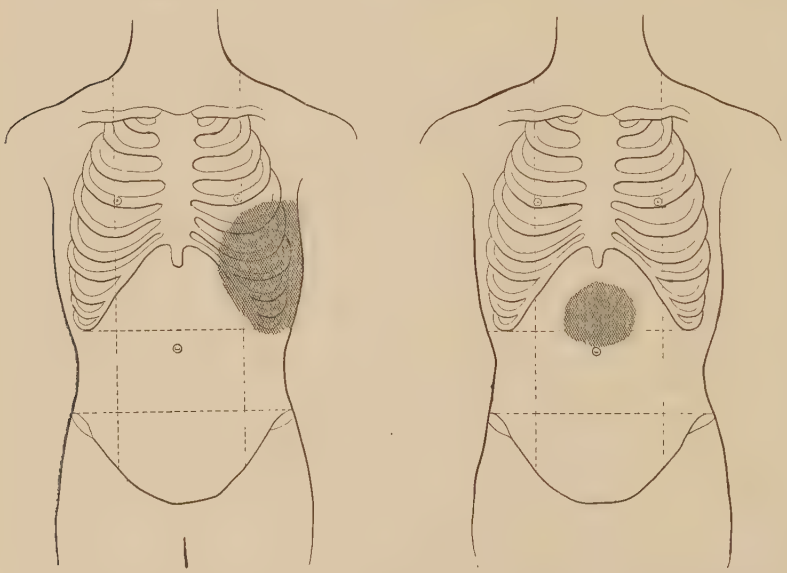


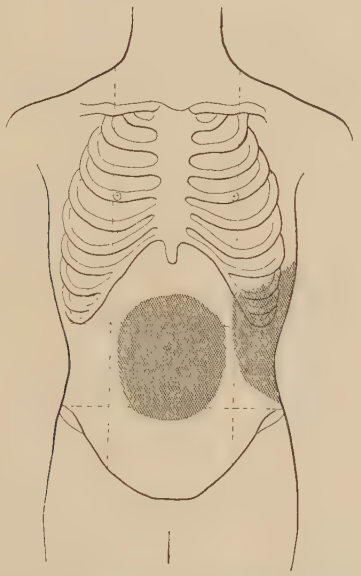
FIG 6.—In this area constant sensation of oppression for seven years ; not associated with the attacks of cramp.

FIG. 7.—This exactly represents situation of pain in attack on October 11th and 12th. None in any other situation.

aggregation of them, together with polymorphonuclear leukocytes. Some twelve examinations of the urine were made from October to the day of the operation. Three of these were voided during an attack. In the latter red blood corpuscles in fair amount were found, more numerous in specimen during and at the termination of an attack. Pus corpuscles, single and in groups, were noted. Mucous and hyaline cylindroids, hyaline casts and a fair trace of albumin were usually evident, as were on several occasions hyaline casts

carrying red blood corpuscles and granular epithelial cells, evidently from the renal tubules. Some four of the specimens were voided in my presence, the urine flushing the urethra being discarded. Crystalline elements were rarely seen in the freshly voided specimens. Only once, and that after rather severe muscular exertion, purposely undertaken for the examination, a glass of hot water being previously drunk and the bladder previously emptied, were free uric acid crystals numerous. Then, as on other occasions, there were a

FIG. 8



Attack lasting forty-eight hours. Onset in centre of abdomen; pain so severe as to "double" him up, diffused to left loin, to the lower dorsal and lumbar region, and left hypochondrium, and finally over whole abdomen.

moderate number of red blood corpuscles and a few hyaline casts. Calcium oxalate crystals were never seen. On several occasions there were noted present in the suspended mucinous sediment, which developed when urine had stood a few hours, a few whitish flakes; these were made up of aggregation of pus corpuscles, with red blood corpuscles and moderate number of ovoid nucleated cells, twice or thrice the size of polymorphonuclear cells. There were also twisted mucinous casts, as if from the ureter, which, on addition of acetic

acid, were found to be made up chiefly of polymorphonuclear leukocytes. Chains of streptococci were also noted in a specimen examined by Dr. Ghriskey.

Operation by Dr. W. W. Keen January 18, 1900. Kidney unusually difficult to reach and impossible to deliver because of dense adhesions binding it to adjacent parts. Section and thorough exploration through the wound; no stone detected. Repeated but ineffectual efforts were made to gain access to the ureter. The kidney did not appear especially enlarged, nor its pelvis dilated. Dr. Keen stated that no blood was noted to be passed in urine after operation, which suggested obstruction of the ureter.

Recovery from operation without complication. Dr. Minich reported to Dr. Keen that on April 1st, ten weeks after operation, patient had the "worst attack he had ever had," requiring $\frac{3}{4}$ grain of morphin, hypodermically, for its relief, and again in June two severe attacks, "the seat of pain being a little to the left of the umbilicus." He has not reported to Dr. Keen or myself since the operation, and repeated efforts since the above report to locate him have been unavailing.

A second exploration of the kidney and by the route and method adopted by Morris, the oblique lumbar,[1] was here regarded as essential, in order to gain free access to the ureter, which the indications are is the seat of partial obstruction from a ureteritis accompanying the perirenal inflammatory process.

In the case to be described the chief points of interest are simulation of stone in the kidney in a neurotic; the subject of severe attacks of left-side loin colic; resultless exploration of the kidney; a second section proposed; a further study excluded stone. Prompt recovery followed a change in the patient's mental condition.

Case VII.—J. P., aged twenty-five years, married, white, American, clerical work, consulted me February 12, 1901; the chief points in the history then elicited were:

The first symptoms of his ailment appeared in June, 1899, with an attack of left-sided renal colic of eight to ten hours' duration; he stated a small stone voided; has had recurring attacks of left-sided

[1] Renal Surgery, Hunterian Lectures, 1898, p. 116.

loin pain since then from once to twice a month, and nineteen such stones observed by him to have been voided. He has recovered several of these, but had, he stated, given them to one of his previous attendants.

In September, 1899, he had gone to the Johns Hopkins Hospital, where he had been an in-patient for some weeks, and was later transferred to the surgical side. He said that he had been *x*-rayed, a large stone noted, and that Dr. Halsted had operated in January, 1900, removing a calculus the size and shape of the thumb, but that ten days after operation the pains recurred as before. Since operation three or four stones passed, following eight to ten severe attacks. Attacks were all very similar. Suddenly appearing severe left-sided loin pain, approximately from loin to abdomen, but no tendency to shoot toward bladder, testicle or thigh. Commonly nausea and vomiting at the height of attack; sometimes delirious; usually requires morphine hypodermically for relief; sitting posture, "chin to knees and head to the left, helpful." Five years before he had had severe attacks of colic, forty hours' duration, in the same situation. Had several hemorrhages, it was thought from the lungs, about this time, but a New York consultant had said from the stomach. No other past or present indication of lung trouble. Has had "chills and fever" every summer for a number of years. Lived for many years in the South. Has had the diseases of childhood; in adult life pneumonia twice; dysentery for six weeks; several accidents; operation for double hernia, January, 1898; no syphilis; no family history of tuberculosis or carcinoma; moderate alcohol but excessive tobacco (cigarettes) indulgence; coffee in excess.

Physical Examination. Lungs normal; heart irritable (coffee and tobacco); no valvular lesion; neither kidney palpable; spleen not enlarged; liver outline normal; stomach slightly myasthenic; inferior border to umbilicus; scar from past hernia operation visible.

Blood examination for plasmodia, negative.

Urine Examination. Voided in laboratory day of first visit, clear, colorless; specific gravity, 1002; no sediment for microscopic examination; albumin absent. February 13th, day specimen: 180 c.c., clear; light amber; acid; specific gravity, 1015; small trace of albu-

min. Centrifuged specimen: scanty sediment; scattered few uric acid crystals; stray red blood corpuscles and leukocytes. February 26th, day specimen: colorless; specific gravity, 1003; no sediment.

In response to inquiry, Dr. Halsted wrote me that he had operated for stone, which he had failed to find, though he thought he had explored the pelvis and calices of the kidney very thoroughly, but that he now could understand from later anatomic study of the kidney how one or more stones might have been overlooked; that no *x*-ray examination had been made; it had been arranged for with Dr. Leonard, Dr. Halsted going to Philadelphia for that purpose. The patient had failed to keep his appointment, instead had gone off and got married.

Dr. Halsted regarded it likely that a stone (or stones) was present and favored a second operation. The Johns Hopkins Hospital medical record of the case prior to operation was interesting. The following is briefly noted from it: He had been in the hospital from September 3 to 29, 1899.

Diagnosis: renal colic. Lately sleeplessness; anorexia; palpitation; flatulency; headache only since doing office work (eye-strain); tendency to moist hands and feet; very active dermatographia; a recent history of dysentery; frequent attacks of "chills, high fever and sweats on alternate days;" said to have been cured by quinine.

Physical examination disclosed no abnormality in chest or abdomen; kidneys not palpable; a series of attacks was observed in the hospital. Chief points noted in first attack were discomfort in the umbilical region, thence to left loin, increasing to pain; very severe; vomiting relieved; no radiation to testicle; no retraction (in one attack retraction noted); no pain on pressure in region of kidney; slight sensitiveness; kidney not palpable. After some hours, the paroxysm continuing, pain suddenly ceased and 1000 c.c. urine voided, "in which a little blood evenly distributed was not apparent until after standing." No attempt to micturate during the attack; free from pain for forty-eight hours. 6 P.M., a second seizure. Discomfort in abdomen and loin; two hours later "vomiting and great pain in left lumbar region; hot bath and morphin; no relief; during spasms of pain delirious." "Pains seemed most severe, but patient afterward had no consciousness of it." "Attack ceased about 3

P.M.; uneasiness continued until 9 A.M. Vomiting frequently preceded spasm or occurred during seizure. Toward the end of series of attacks marked neurotic element." "Voided no urine since 6 P.M. last night (September 12th) until 3 P.M., then 1200 c.c.; no blood; no gravel." "September 17th, patient has had a number of attacks very similar to those of September 12th. Early during the attack 1000 c.c. urine voided. After passing a considerable quantity flow suddenly stopped. In about fifteen minutes a little muscular spasm felt, but no pain; then a few drops of blood from penis. Flow of urine again natural. Testicles retracted; attempts to micturate once or twice during the attack unsuccessful."

Three records of urine examinations: September 9th: "1000 c.c., clear; neutral reaction; pale yellow; specific gravity, 1007; trace of albumin; cloudy sediment; stringy pink; red blood corpuscles numerous." "September 10th: 1040 c.c., clear; amber; faintly acid; specific gravity, 1018; mucus cloudy; calcium oxalate in clumps; occasional pus cells. September 17th: 1040 c.c., turbid; pale yellow; faintly acid; specific gravity, 1012; albumin, trace. Sediment, mucous cloud; red blood corpuscles and pus cells numerous. Exploratory nephrotomy: Section left kidney; thorough exploration of pelvis. No stone found; no abnormality noted. Typical attacks of renal colic."

I regarded the case as probably renal calculus, which had been overlooked in operation, and in this opinion Dr. Halsted himself, in a personal letter, coincided. Two skiagraphs taken by Dr. Leonard were negative. Patient admitted to my service at the Episcopal Hospital for observation. Here he remained several weeks in a private room. Out-of-door privileges. A number of observed attacks were similar in outline to those noted occurring at the Johns Hopkins Hospital; seizures lasted from a few hours to a day or two; pain apparently of intense severity in some; at times delirious. Urine suppressed for twelve hours; then a large quantity of very low gravity voided. Morphin demanded for relief of pain, but hypodermic injections of water alone in later ones efficient. States he passed several small stones in the public urinal during sojourn at the Episcopal Hospital, which he could not recover. Many urine examinations were practically similar to the foregoing. At the end

of seizure, volume usually large. Gravity low. In interval, average gravity 1015 to 1021; usually clear; amber; acid; and occasionally stray red blood corpuscles. Tubercle bacilli looked for resultlessly. On one occasion, shortly before he left the hospital, and on another day after he stated he had passed a small stone, specimen of urine asked for by Dr. Ghriskey in hospital laboratory. The patient took the glass into an adjacent room; specimen furnished was visibly blood-stained. Dr. Ghriskey noted a drop of bright-red blood on the patient's handkerchief. It was believed he had pricked his finger and introduced blood into the urine. Several blood examinations (from finger) had been made in this case, and he had been in the habit of watching the work done in the laboratory, and often seen blood so taken from patients for examination.

There is a record of twelve urine examinations made by Dr. Ghriskey, of single specimens, and of the twenty-four hours' urine during the seizures, at their termination, and in the interval. In all the centrifuge was employed; but twice were (stray) red blood corpuscles noted. On two occasions the urine was markedly bloody, but in the light of present knowledge it is believed, as above remarked, to have been tampered with.

Despite the negative finding of the *x*-ray, Dr. Halsted, who was communicated with on several occasions while the patient was in the hospital, believed stone present, and favored a second exploration. This the patient was apparently agreeable to; it was in contemplation when he suddenly, without previous notice, disappeared from the hospital, leaving his wardrobe, including even his watch, and he was not heard from for some time.

Certain features about the seizures, a strong neurotic element frequently manifest, including the relief obtained during the attacks by water hypodermics; the curious retention of urine for a day or so without discomfort; the passage of a large quantity of a gravity approaching water; many discrepancies and inconsistencies, and actual attempts at deception in his statements as to past and present attacks, including the asserted passage of calculi, had caused us in the hospital to not only recognize a strong emotional element in the case, but to question if that were not the whole feature. The subsequent history practically demonstrated the correctness of this view.

The patient was dissatisfied with his previous clerical occupation, and there were several elements in his domestic life that would readily serve to aggravate a neurotic tendency. He had an opportunity through influential friends to enter the regular service of the army, in which he had during the Spanish War been a volunteer officer, and the life appealed strongly to him. On leaving the hospital he had gone to Washington; successfully passed the civil service and the medical examinations, and received an appointment. I lately heard from a kinsman of his who had originally sent the case to me, that he had been constantly in active duty, and from the time of his appointment had remained in good health, and was totally free from these attacks.

This case has been narrated somewhat in detail because of its unusual features. Here apparently pure hysteria so mimicked the features of renal calculus that his many attendants were deceived. An exploration of the kidney had been done with his ready acquiescence, and the second had been contemplated. The attacks of unilateral colic were undoubted, but they were apparently, as the later history showed, an expression of hysteria. To give verity to and emphasize the ailment which the patient himself regarded as kidney stone, he had wilfully misled in stating that he had passed calculi, as he had attempted to deceive in first relating his history—that he had been *x*-rayed while under Dr. Halsted, and a large stone seen, describing the shape and size of the suppositious stone removed. He is believed to have similarly deceived on more than one occasion in introducing blood into the urine specimen for examination.

DISCUSSION.

Dr. Danforth: As regards the *x*-ray, my experience has been very much like Dr. Stewart's; it is sometimes very valuable and sometimes valueless or even misleading. A great deal depends upon the skill and experience of the operator, and quite as much also upon the experience and acumen of the surgeon who interprets the skiagraph. But I have not risen for the purpose of discussing Dr. Stewart's paper, but chiefly for the purpose of showing a remarkable collection of calculi which were the product of a single patient. I show you here a calculus removed from the bladder of a young

lady, twenty years old; it weighed seven and one-half ounces, and was covered with a thick layer of red granulations at the time of removal. About two years later she came under my care, and I removed the large irregular calculus which I now show you from the right kidney. She died a few days after of sepsis and exhaustion, and the unusually large calculus, which I now show you, was removed from the left kidney postmortem. The most remarkable thing about this case is the almost entire absence of pain until the last few weeks of the patient's life, notwithstanding the presence of these large, rough and irregular calculi in the kidneys.

Dr. Stewart: I should like to ask Dr. Danforth whether the *x*-ray was used in the case he reports?

Dr. Danforth: No, the *x*-ray was not used. The case I report only goes to show what a Western girl can do when she tries, even in the production of stone.

Dr. Tyson: I have had some experience with cases simulating stone in the kidney as well as of actual stone in the kidney. The former are decidedly more interesting. A number of these were operated on without finding stone. In some instances exploration by the *x*-ray preceded operation, on others it did not. In the last two operations occurring in the past fifteen months there was found a condition which, it occurred to me, might explain the symptoms. Both of these cases were attended by tenderness in the kidney, with an intermittent or remittent catarrhal condition of the urine—viz., a moderate amount of leukocytes, a mere trace of albumin. In both of these cases there was what might be called a capsulitis; that is, the capsule of the kidney was very closely adherent to the organ and was depressed in places in a cicatricial manner. In both cases the kidney was decapsulated. Both were followed by recovery. A similar condition might have been found by closer inspection of other cases operated upon, but it did not occur to those concerned to look for it. In the future I shall bear this in mind, and now very strongly advise the examination of the kidney with a view to this particular relation of the capsule. It is as though the capsule compressed the kidney, and in this way produced the phenomena of stone, especially pain and tenderness.

Dr. Forchheimer: I have seen three cases of this sort in which tenderness and other symptoms of renal calculus were present, and yet the urinary analysis showed nothing significant. All of these patients were operated on. In two of them the *x*-ray was used. The first was before the time of the *x*-ray. Nothing was found. The last was in the case of a girl about twelve years of age; she had been operated on for appendicitis and the appendix was removed; the symptoms did not disappear, and the pain and tenderness

continued. Finally, we used the *x*-rays and there were some indistinct shadows produced that seemed to show that the trouble was in the right ureter. The patient was operated on with the idea that a calculus would be found in the right ureter, but I had my doubts beforehand of the accuracy of the *x*-ray diagnosis. Reyer, in his great book on *Diseases of the Kidneys*, has described the same condition and given to it the name of perinephritis. In the last case I suggested that it was undoubtedly a case of perinephritis, and when we came to operate upon the kidney we found that condition. There was much thickening simply in the capsule. All made excellent recoveries; one of them has been well for nine years.

Dr. Billings: The presence of microscopic blood in the urine with pain in the right belly is considered important as a diagnostic sign in stone of the kidney. In acute appendicitis microscopic blood is not infrequently found in the urine, and therefore the presence of blood in the urine in cases of pain is not always a good differential sign between stone in the kidney and some other conditions.

x-ray pictures of the urinary apparatus, even when they show a possible shadow of a stone in the ureter or bladder, are not necessarily positive evidence of a calculus. The interpretation of shadows by lay *x*-ray operators is also sometimes misleading. In a case under my own observation the shadow interpreted as a stone in the bladder by the *x*-ray operator proved to be the bulb of a large uterine pessary.

Dr. Stewart: About the matter of the presence of microscopic blood in the urine: The importance of the presence of blood corpuscles in the urine in cases of suspected stone is its persistence over long periods. Concerning the matter of perinephritis, in one of the cases I report the symptoms were originated by the presence of dense perinephritic adhesions. In this case in addition to the presence of fairly frequent blood cells there were streptococci. There had been an injury to the kidney with subsequent infection. It is now well recognized that one has to be particularly careful in regard to the *x*-ray diagnosis of ureteral stones. Small shadows of unknown origin are sometimes cast which have been mistaken for stones, and recently Dr. Brewer reported a case in which a calcified tip of an appendix epiploica had been mistaken for a ureteral stone, and which he (Dr. Brewer) regarded as but one of a number of different origins for the extraureteral concretions.

CHYLOUS AND CHYLIFORM EFFUSIONS INTO THE SEROUS SACS: WITH A CASE.

By J. C. WILSON, M.D.,
OF PHILADELPHIA.

The subject of effusion of chyle, chyle-like and fatty fluids, has been especially investigated in this country by Busey, whose papers contain full studies of the early literature of the subject and important collections of cases. The paper read by Dr. Busey before this Society in 1889[1] contains a table of 33 collected cases of "effusion and accumulation of chyle and chyle-like, milky, fatty and oily fluids in the peritoneal cavity," together with abstracts of 13 cases collated after the table was prepared. In Germany, Quincke (1875),[2] Bargebuhr (1893),[3] and again (1895),[4] Rotmann (1897),[5] Mutermilch (1902)[6] and others have published valuable papers upon the subject.

To Quincke is due the credit of having first pointed out the distinction between chylous and chyliform effusions—hydrops chylosus and hydrops adiposus—while Bargebuhr recognized the important fact that a nice distinction between these two forms of effusion cannot in all cases be made, and that in some cases the presence of the chylous transudate and the chyliform exudate at the same time is by no means improbable—*gar nicht undenkbar sei.*

Bargebuhr collected 126 cases, including Busey's cases, reported between 1633 and 1894.

Rotmann's collection of 29 cases includes some that were overlooked by Bargebuhr and those published subsequently, making

[1] Trans. of Asso. Amer. Phys., vol. iv. p. 76; Amer. Jour. Med. Sci., vol. xc. p. 373.
[2] Deutsches Archiv. f. klin. Med., Bd. xvi., 121–139.
[3] Ibid, Bd. 51, 161–192.
[4] Ibid, Bd. 54, 410–441.
[5] Zeitschrift f. klin. Med., Bd. xxxi., 416–441.
[6] Ibid., Bd. 46, 123–134.

155 in all to 1897. Of the latter 3 were personal observations made in Mosler's clinic.

Since the date of Rotmann's paper many cases have been reported.

It is certain that the frequency of chylous and chyliform effusions is far greater than the literature indicates. The appearance of the fluid is striking, and at once arouses the attention of the trained observer; yet it presents in some cases a superficial resemblance to pus, which may mislead the physician whose attention has not been especially called to the subject. There are no means by which the nature of the effusion may be determined *intra vitam* except by the withdrawal of a portion of it. In many of the reported cases its presence was first recognized at the autopsy. The fact that cases occur much more frequently than the collected statistics indicate is evident upon the consideration of the experience of those who have written upon the subject. Senator saw 8 cases, Rotmann saw 5 cases at Greifswald in the course of two years, and I have seen in all 3 cases. Not all the cases by any means find their way into the literature, for the reason that many observers hesitate to report single cases and the cases which recover, and those in which autopsy cannot be made are necessarily incomplete.

Rotmann's study of 155 cases shows the effusion to have been present in the abdomen in 104 cases, in the pleural cavity in 49 cases, and in the pericardium in 2 cases. In certain cases, as in that which forms the basis of this communication, the milky effusion has been found both above and below the diaphragm.

The pathologic causes of milk-like effusion into the serous sacs are, in general: 1, trauma; 2, tuberculosis; 3, malignant disease; 4, filariasis; 5, thrombosis of the left subclavian vein; 6, disease of the liver; 7, syphilis.

The particular causes of such effusions into the peritoneal sac (*chylous ascites*) comprise those conditions which produce a solution of continuity in the vessel walls by injury, inflammation or extreme tension, or by transudation through the wall weakened by disease. Under this heading Rotmann has grouped the following special causes in the order of their frequency: compression

of the thoracic duct or the lymphatic vessels by glandular enlargements, neoplasms, etc., 17 cases; non-tuberculous peritonitis, 9; occlusion of the left subclavian vein, 6; excessive pressure, strain, cough, 5; peritoneal carcinoma, 5; filariasis, 3; occlusion of the thoracic duct, 3; occlusion in lymph glands, 3; occlusion of lymph vessels, 2; external pressure, 2; malignant lymphoma, 2; disease of the liver, 2; syphilis, 2; primary disease of the lymph vessels: angioma, 1, and calculus in the receptaculum chyli, 1.

The special causes of *chyliform effusions* into the peritoneal sac he groups as (*a*) due to fatty changes in cells, especially endothelial, and the cellular elements of new growths. Tuberculosis, 6; carcinoma, 5; cirrhosis of the liver, 3; cardiac disease, 2; sarcoma, 2; chronic non-tuberculous peritonitis, 1, and an apparently primary fatty degeneration of the endothelium, 1; and (*b*) an abnormal fatty condition of the blood lipemia, 1.

The special causes of *mixed forms* are, according to this observer, carcinoma, peritoneal, mesenteric, glandular, etc., 3, and tuberculous peritonitis, 1.

The special causes of *chylous effusion* into the pleural sacs are (*a*) those leading to the escape of chyle as the result of injury or disease of the vessels, namely, external violence, 8; carcinoma of the pleura, 5; occlusion of the left subclavian vein, 4; compression of the duct by tumor, 2; malignant lymphoma, 2; disease of the lymphatic vessels, sclerosis, lymphangiectasis, 2; occlusion of the thoracic duct, 1; filariasis, 1, and excessive strain, 1; (*b*) the discharge of a chylous ascites into the pleural cavity by way of the lymph spaces, 1.

Rotmann groups the causes of *chyliform effusions* into the pleuræ as (*a*) the presence of cells that have undergone fatty degeneration, as in carcinoma of the pleura, 5; tuberculous pleurisy, 3; non-tuberculous exudative pleurisy, 3, and abscess of the lung, 1, and (*b*) abnormal fat in the blood, lipemia.

The two cases of fatty effusion into the pericardium in the series he attributes to rupture of chylous vessels (?) and the discharge of chyliform fluid from the left pleura by way of the anastomotic lymph channels. In twenty-five of the cases no satisfactory cause could be determined.

It is obvious from a review of the above facts that in a considerable proportion of the cases the causal conditions are such as to produce both chylous and chyliform products, and the conclusion is inevitable that both these factors must be present in many milky effusions, and that such fluids are often mixtures in varying proportions of transudates and exudates.

The chemical and morphologic characters of milk-like effusions have been especially studied by Mutermilch. The investigations of this observer were conducted upon the fluid obtained by puncture in the case of a child aged five months, in whom a right-sided pleural effusion followed a fall from the mother's bed.

The quantity of the fluid withdrawn was 115 c.c. It presented the following characteristics:

A complete resemblance to milk; opaqueness; absence of odor; whitish color, with a faintly yellowish or creamy shade; feeble alkalinity; specific gravity, 1017. Upon microscopic examination there were seen great numbers of minute dust-like granules in active, molecular movement. Here and there were slightly larger bodies, constituting distinct points scattered separately or in groups; a few leukocytes; larger cells containing distinct, highly refractive granules and erythrocytes in very small numbers and only found upon careful search.

The chemical examination, conducted upon the hypothesis that the fluid was a fat emulsion, yielded the following results:

Shaken with ether in a test-tube the fluid became less opaque. When a few drops of potassium hydroxid were previously added it became quite transparent and almost colorless. Upon the addition of osmic acid the fluid became blackish.

Microscopically, upon the addition of a 1 per cent. solution of osmic acid to a drop of the fluid, the dust-like granules assumed a dark-gray color. The same change in color was observed in the granules in the large cells. Upon the addition of ether the dust-like granules were dissolved. They ran together and formed at first smaller, then progressively larger, and finally, quite large, highly-refracting globules, which, upon treatment with osmic acid solution, became black in color.

The fluid, upon standing, deposited upon the bottom of the

vessel grayish-red flocculent masses, in which were to be seen under the microscope the above-described morphologic elements.

The morphologic elements were almost exclusively leukocytes and in marked preponderance lymphocytes. There were present in small numbers neutrophilic leukocytes containing fat granules, together with endothelial cells and a very few red blood corpuscles.

The chemical examination yielded the following results—100 c.c. of the fluid:

Solids	8.360
Albumin	6.135
Extractives by ether	1.481
Cholesterin	0.174
Soluble salts	0.563
Insoluble salts	0.028
Extractives by water	0.132
Extractives by alcohol	0.121

The fluid was absolutely sterile, neither microscopic nor by culture upon bouillon and agar were any micro-organisms to be recognized.

The above characters of the effusion in Mutermilch's case, considered in connection with the etiology of the condition—traumatism—and the entire absence of symptoms suggestive of pleural inflammation, justified the conclusion that the fluid consisted of chyle.

Quincke was the first to divide the fatty effusions into two groups: First, those consisting of chyle from the thoracic duct, or the lacteals—transudates—and, second, those resulting from fatty metamorphosis of the cellular elements in inflammatory effusions—exudates. It was generally thought that these two forms of milky fluid could be differentiated only by the microscope. Quincke described a case in which there was escape of chyle into the pleural cavity. The fluid was like milk, with a slightly yellow shade. Under the microscope it showed minute granules of different size, but all in the form of apparently round points, or dust particles, and a very small number of white blood corpuscles.

In contrast to this chylous effusion he described the form of fatty fluid resulting from fatty changes in the morphologic elements. The fluid was bright yellow, somewhat cloudy, whey-like. Upon standing there formed upon the surface a thin,

cream-like layer, showing under the microscope small globules, mostly in the form of collections of highly refractive granules, less frequently having sharp borders, and still less frequently presenting the appearance of large, indistinct nuclei. In the fluid underlying this layer were seen white blood corpuscles and larger round cells, which, in consequence of differences in the amount of fat, presented all possible transition forms. In this case Quincke ascribed the presence of the fat to the breaking down of cellular elements. He designated the effusions of the first category as hydrops chylosus; those of the second category as hydrops adiposus.

In 1885 Senator[1] adopted Quincke's division of the fatty effusions into hydrops chylosus and hydrops adiposus. Since the cases in the second category result from the fatty metamorphosis of endothelial and other cellular elements, and the diagnosis rests upon the presence of cells in which the fatty changes are incomplete, it is obvious that in advanced cases, in which the transitional forms may not be found, the diagnosis of the nature of the effusion must remain obscure. For this reason Senator ascribed great importance to the chemical study of these fluids, and especially to the presence of grape-sugar, holding that chyle and lymph contain sugar constantly in quantities which may be easily recognized, while this substance is only found in serous transudates and exudates in non-diabetics exceptionally and in traces. Grape-sugar, in more than doubtful traces, was believed by this author to indicate the presence of chyle. Later investigations, especially those of Pascheles and Reichel,[2] Pickardt,[3] and Rotmann,[4] have established the fact that ordinary serous transudates and exudates often contain this substance in recognizable quantities, and that its presence in chyliform exudates may also be expected.

Straus[5] was able to demonstrate the chylous nature of the fluid in fatty ascites by giving his patients a diet rich in fat, the administration of which was found to greatly increase the proportion of the fat in the peritoneal fluid. This observer regarded the rapid

[1] Charite-Annalen, 1885, S 307.
[2] Wien. klin. Wochenschr., 1896, No. 17.
[3] Berl. klin. Wochenschr., 1897, S. 844
[4] Münch. med. Wochenschr., 1898, No. 6.
[5] Archives de physiol. norm. et patholog., 1886, p. 367.

renewal of the fatty fluid having always the same peculiarities as indicating its chylous nature.

The milky effusions into the serous cavities do not always owe their characteristic appearance to fat. Micheli and Mattirolo[1] have described pseudochylous forms of ascites, and have satisfied themselves experimentally that in the cases which they had under observation the milky appearance arose from the presence of lecithin.

Dr. Edsall reported at the last meeting of the American Pediatric Society a case of Hodgkin's disease, not yet published, in which there was a non-fatty pleural effusion, the opacity being due to altered globulins.

The case about to be described, brought to me by Dr. Housekeeper, of Vandengrift, Pennsylvania, illustrates one of the more common forms of fatty effusion into the serous cavities. It may, I believe, be properly regarded as an example of that group of cases in which the effused fluids, though fatty, are neither chylous nor chyliform or chyloid, but a mixture of both. This opinion is based upon the following facts:

1. The constant gross physical characters of the peritoneal fluid and that removed from the left pleural cavity upon repeated aspiration on several occasions at comparatively short intervals of time.

2. The practically identical microscopic and chemical characters of the two specimens of left pleural effusion examined by Dr. Kelly and obtained within a period of twelve days.

3. The presence in those fluids of fine dust-like granules in great numbers, and showing active molecular movement and lymphocytes, together with polynuclear neutrophiles, nuclei and endothelial cells in various transitional stages of fatty change.

4. The different gross and microscopic characters of the fluid contained in the circumscribed right pleural effusion.

5. The underlying pathologic conditions, namely: diffuse sarcoma of the retroperitoneal and thoracic lymph glands and inflammatory pleural changes.

[1] Wien. klin. Wochenschr., 1900, No. 3, S. 56.

6. The softened condition of the lymph glands in the neighborhood of the receptaculum chyli, and the fact that the walls of that structure could not be recognized upon careful search and the thinned walls of the thoracic duct, changes permitting the escape and transudation of chyle.

7. The inflammatory changes about the sarcomatous glands and the pleural inflammation, the source of proliferation of endothelial cells and serofibrinous and seropurulent exudate, with fatty changes in its cellular elements.

Sarcoma of retroperitoneal and thoracic lymph glands; fatty ascites discovered upon operation for hernia; double pleural effusion, fatty upon the left side and presenting upon repeated aspiration, at intervals extending over a period of many months, the same appearance; circumscribed and seropurulent upon the right side; microscopic and chemical notes on the fluids; autopsy.

Anamnesis. A. M. B., female, aged thirty-five years, single, a teacher; admitted to private room in the German Hospital December 5, 1904.

Family history good; father living and well; mother died about the menopause from disease the nature of which is unknown to patient; only two brothers, who are living and in good health; no sister. No history of tuberculosis or malignant disease could be obtained.

The patient states that she had scarlet fever in childhood but cannot tell whether or not she had the other diseases of childhood. She had a severe attack of tonsillitis at the age of fifteen, but always regarded herself as having good health until about three years ago. Until that period had a good appetite and digestion and regular bowels. First menstruated at fourteen, and that function has been regularly and painlessly performed until the present time. Dates her illness from the appearance of a femoral hernia upon the right side in the spring of 1902. This speedily began to give trouble, which led to an operation shortly afterward. In reply to a note of inquiry which I wrote to her surgeon, Dr. J. J. Buchanan, of Pittsburg, I received the following reply: "I operated on Miss A. M. B. for the radical cure of a femoral hernia with irreducible omental contents if I remember aright. The peritoneum contained a considerable quantity of free fluid which was opaque, milky or deep straw color. I remember that she was turned on her side to allow it to flow out. Perhaps there was a pint or two. No tubercles were on the sac or presenting omentum. She had no fever before or after the operation. Her wound healed *per primam.*"

The fluid was thought to be that of a tuberculous peritonitis. I was unable to ascertain whether or not a systematic examination of it had been made.

The following autumn she began to be short of breath upon exertion and had during the winter four severe attacks of bronchitis. In July, 1903, she

had another attack of bronchitis. In the intervals between these attacks she had occasional slight cough but little or no expectoration, but felt constantly oppressed and was very short of breath upon even moderate exertion. At the close of the last attack of bronchitis the presence of a left pleural effusion was recognized and paracentesis was performed and a quantity of fluid, milk-like in appearance, withdrawn. This operation has been repeated a number of times, in all, as follows:

1903, July.	Quantity withdrawn about	. . . . .	. . .	1000 c.c.
1904, July.	"	"	"	. . . . .	. . .	1000 c.c.
1904, Oct. 1.	"	"	"	. . . . .	. . .	2000 c.c.
1904, Oct. 15.	"	"	"	. . . . .	. . .	2500 c.c.
1904, Nov. 1.	"	"	"	. . . . .	. . .	2500 c.c.
1904, Dec. 2.	"	"	"	. . . . .	. . .	2500 c.c.

The fluid always presented the same appearance and corresponded, according to the patient, to that which was removed after she came under my observation, and is fully described in Dr. Kelly's report which follows. During this period the patient occasionally noticed a slight discharge of similar fluid from the scar in her thigh resulting from the operation for the radical cure of the hernia. Her urine has never been milky in appearance. About the time that the first aspiration of the chest was performed her cough ceased and has not recurred. She has had no chills, fever, night sweats, headache or pain. Two years ago she weighed 128 pounds. Her present weight is 108 pounds.

Status Presens. A tall, slender, well-formed woman of good color but slightly cyanotic on exertion. No dropsy or edema; no cutaneous eruption. Temperature normal, at times slightly subnormal, chest somewhat flattened on both sides, but more upon the left than upon the right. Respiratory movement shallow, the excursus being much more limited upon the left than upon the right side. Respiration frequency while at rest 20, upon slight exertion rapidly increased to 30 to 36.

The impulse of the heart not well made out either upon inspection or palpation. It is interesting to note in view of the postmortem findings that careful palpation and auscultation failed to reveal any signs of a mitral stenosis. In the precordial area there was no thrill, nor was any murmur to be heard. There is accentuation of the second sound at the base, particularly in the pulmonary area. The pulse is small and of moderate tension. Its frequency varies in repose from 80 to 96.

The percussion resonance is clear on both sides anteriorly in the infraclavicular regions with a slight tympanitic quality upon the left side. Below this it is impaired upon the right side and there is dulness below with flatness at the base upon the left side. The percussion signs posteriorly correspond to those in front except that dulness (flatness) extends much higher and there is flat tympany at the upper part of the chest. There is partial obliteration of Traube's semilunar space.

Upon auscultation feeble vesicular and bronchovesicular respiration over

the upper lobes, but no rales. At the right base posteriorly a few faint subcrepitant and crepitant rales, especially upon deep inspiration. Over the area of dulness on the left side absent breath sounds diminished vocal resonance. There is absence of vocal fremitus. No friction sounds except in a limited area at inner border of left scapula. The area of liver dulness not enlarged. Its lower border corresponds to the margin of the ribs in the midclavicular line and descends about two fingers' breadth upon full inspiration.

The lower border of splenic dulness is below the costal margin.

The abdomen is soft, elastic and symmetric. The presence of ascites cannot be made out.

Urine amber, acid, 1030; no albumin, no sugar; phosphates, epithelial cells, leukocytes and bacteria. Amount measured 400 to 900 c.c. Some lost at stool.

Blood: hemoglobin, 90 per cent.; erythrocytes, 6,325,000; leukocytes, 7200.

Repeated examination both by day and by night showed no filaria.

Operation December 19, 1904, by Dr. Deaver. A large portion of the thoracic fluid was removed with aspirator. An incision 12 cm. long was parallel to and over the eighth rib, its median portion corresponding to the midscapular line. Rib exposed and intercostal vessels raised upward; a bone elevator placed under rib and about 5 cm. removed with lion-jawed forceps. A similar portion was excised from rib above. Intercostal vessels ligated. Thoracic cavity opened, a quantity of chyloid fluid evacuated with force. Not all the fluid was removed. A large rubber tube (short) was anchored in the incision with silk. Incision was closed up to the tube with catgut. Antiseptic dressing.

For a time after the operation the patient did well, the temperature remaining normal. Beginning upon the tenth day the temperature became irregular, at times reaching 102° or 103° and falling again to normal. The patient became dyspneic and somewhat cyanotic with rapid pulse, which upon January 1st became uncountable. Upon January 3d the temperature rose to 103° and the patient gradually sank, dying at 5.30 A.M.

The following is Dr. Kelly s report of his examination of the fluid removed from the left pleura December 8, 1904:

The fluid quite resembles milk in ordinary appearance—being whitish or slightly yellowish, opaque and odorless. Its specific gravity is 1017. It contains a considerable amount of albumin—roughty, about 4 per cent. It does not respond to the ordinary tests for sugar—copper solutions, phenylhydrazin and fermentation tests. The addition of ether followed by vigorous agitation, causes the fluid to clear somewhat; the previous addition of a few drops of potassium hydroxid causes it to become much clearer. The addition of osmic acid causes the fluid to become quite blackish. On standing sometime a slight fibrinous deposit settled at the bottom of the vessel, and a small layer resembling the cream that forms upon milk formed at the surface. After

standing in stoppered test-tubes and flasks at room temperature for ten days and two weeks, and being in the mean time several times exposed to the air, the fluid appeared quite "sweet."

Microscopically the fluid consists of cells (the character of which will be discussed presently) and a very large number of the finest granules; occasionally a single or several larger granules are observed, but almost all are very fine, even dust-like. They exhibit considerable molecular movement. The addition of a few dops of 1 per cent. osmic acid solution to the microscopic preparation causes the free granules, as well as similar granules in the underdescribed cells, to become darkish, blackish-gray in color. The addition of ether results in solution of the granules and their confluence to form larger masses, which become discolored, blackened, on the addition of osmic acid.

In addition to the granules, the fluid contains a moderate number of cells, a differential count of which reveals the following: lymphocytes, 76 per cent.; large mononuclear cells, 22 per cent.; polynuclear neutrophiles, 2 per cent.

The lymphocytes conform in all particulars to the lymphocytes of the circulating blood, and the polynuclear neutrophiles are also readily recognized as identical with the predominating leukocyte of normal blood. The cells described as large mononuclear differ somewhat in appearance among themselves. A few of them resemble the lymphocytes, though they are larger; others recall the large mononuclear leukocyte of normal blood; but on account of the presence in the cells of granules resembling and behaving toward ether and osmic like the free granules of the fluid, of vacuolation, and of degenerative changes, it is impossible to say what some of these cells are. Other cells, however, are roundish in outline, vary somewhat in size, have a fairly large, usually eccentric nucleus; their protoplasm contains fatty granules and vacuoles; evidently they are desquamated endothelial cells.

Appropriate staining methods failed to reveal any bacteria in coverslip preparations.

By culture methods a large unidentified spore-bearing bacillus (probably contamination) was isolated.

The results of the examination of a second specimen of fluid received December 20th was identical with the foregoing (except that one portion was slightly pinkish, owing to the admixture of blood).

Almost daily examination of the blood (by day and by night) between December 8th and 20th failed to reveal filaria sanguinis hominis.

A specimen of the fluid was handed to Dr. Charles A. Fife, of the William Pepper Laboratory of Clinical Medicine, for chemical examination. He reports as follows: The fluid is faintly alkaline to litmus paper, but acid to phenolphthalein, requiring 20 c.c. of a one-tenth normal sodium hydroxid solution to neutralize 100 c.c. of the fluid. The specific gravity is 1016.4.[1] The fluid consists of 93.388 per cent. water and 6.61199 per cent. solids, of

[1] Determined by a more sensitive instrument than was used in the other examination.

which 4.679 per cent. is albuminous (probably entirely serum albumin), 1.065 per cent. fats, and 0.5639 per cent. ash. The fluid after the removal of the fats and proteids reduces copper slightly, but does not respond to the phenylhydrazin sugar tests.

The following are the notes of the necropsy (No. 735), made by Dr. A. O. J. Kelly January 3, 1905, six hours after death:

The body is that of a fairly well developed female subject with gracile bony development, slight musculature, and slight panniculus adiposus. The skin is pale; the nutrition poor. There is slight postmortem rigidity, but no postmortem lividity. In the right groin there is a linear scar (the result of an operation for femoral hernia). Posteriorly in the left thorax there is an opening into the pleura, a defect of a rib (due to resection), and a rubber tube draining the pleura. The preperitoneal adipose tissue is slight in amount. The thoracic and the abdominal viscera have their normal relations the one to the other. The left pleura is non-adherent, except for a small area on the diaphragmatic surface; it contains 200 c.c. of rather thick "milky" fluid; in general it is pale, cloudy and thickened, being in some places from 2 to 3 mm. thick; and it is covered (both the parietal and the visceral layers) with a rather thick or viscid, whitish, opaque, "milky" exudate. The left lung is small and compressed, and weighs 400 gm. It is mottled, grayish-black in color, of increased consistency, contains less air than normally, and reveals slight hypostatic congestion. The section surface is smooth, moist and glistening, pale grayish in color, and exudes considerable frothy fluid. The lung crepitates throughout, and contains no tubercles and no cavities. The bronchi contain some serous or mucous fluid; their mucous membrane is pale, their caliber normal, but about them and extending somewhat into the adjacent tissue there is apparently a slight amount of peribronchial connective-tissue overgrowth. The right pleura is dull, cloudy, pale, thickened and universally adherent. As far down as the fourth rib the adhesions are firm and quite obliterate the pleural cavity. Below the fourth rib the adhesions are not so firm, and instead of obliterating the pleural sac give rise to the formation of sacculi containing fluid; between the inferior surface of the lung and the diaphragm there is a large collection of fluid displacing the lung upward, but the lung extends down over the fluid dome-like—its edges reaching well down anteriorly, laterally and posteriorly. The pleura contains a total of 550 c.c. of fluid, which although somewhat "milky," is more correctly dull-grayish in color, opaque and "thinner" than the fluid obtained from the left side. The right lung weighs 650 gm. It is mottled grayish-black in color, of increased consistency, contains less air than normally and reveals slight hypostatic congestion. The section-surface is smooth, moist and glistening, pale grayish in color, and exudes considerable frothy fluid. The lung crepitates through and contains no tubercles and no cavities. The bronchi contain some serous or mucous fluid; their mucous membrane is pale, their caliber

normal, but about them and extending somewhat into the adjacent tissue there is apparently a slight amount of peribronchial connective-tissue overgrowth. A few of the peribronchial lymphatic glands are quite small, firm and anthracotic, and reveal no deviations from the normal; the great majority of them, however, are much enlarged, some of them very much enlarged, pinkish in color and softened—almost diffluent. The pericardium contains 30 c.c. of clear, amber-colored fluid, and is non-adherent throughout. The heart is dilated, somewhat rounded in shape and weighs 230 gm. It, more especially the right side, contains considerable dark clotted blood. The left auricle, the right ventricle and the right auricle are dilated, especially the right auricle. The mitral orifice is contracted, and the leaflets thickened, indurated and shortened. The chordæ tendinæ are also thickened and shortened. The tricuspid orifice admits three fingers readily, and the valve leaflets are probably insufficient. The aortic and the pulmonary valves are normal. The left ventricle measures 8 to 13 mm. in thickness, the left auricle 2 to 4 mm., the right ventricle 5 to 8 mm., and the right auricle 1 to 2 mm. The heart is pale, brownish-red in color and firm in consistency. The coronary arteries are normal. The arch of the aorta and the descending aorta are slightly thickened in patches. The esophagus is normal. The omentum is normal in size and slightly fatty. The peritoneum is dull, cloudy, pale, and slightly thickened in places, especially the peritoneum of the anterior abdominal wall and that of the posterior peritoneal cavity toward the vertebræ near and extending into the pelvis. It is non-adherent throughout. It contains 1200 c.c. of grayish-white, opaque, "thin" fluid. The liver measures 27 x 18 x 5.5. cm., and weighs 1340 gm. It is normal in shape, of increased consistency, smooth on the surface, and has sharp edges. The section-surface is smooth, glistening and moist, mottled yellowish-brown (nutmeg) in color, and exudes an increased amount of blood. The gall-bladder is normal in size, contains fluid bile; the cystic, the hepatic and the common bile-ducts are patulous. The spleen measures 11.5 x 6 x 2.5 cm., and weighs 90 gm. It is dark in color; the section-surface is smooth; and the trabeculæ are slightly increased. The right kidney measures 10 x 5.5 x 3 cm., and weighs 130 gm. The capsule is slightly adherent, and when stripped leaves a slightly granular surface, dark in color. The kidney in general is of increased consistency. The cortex is 7 mm. in thickness. The left kidney measures 11 x 5.5 x 3 cm., and weighs 150 gm. It is similar to its fellow in appearance. Both ureters and both adrenals are normal. The urinary bladder and the external and the internal genitalia exhibit no deviations from the normal aside from the ovaries which are slightly enlarged, whitish, firm and cystic. The stomach is normal in size and position; its mucous membrane is slightly congested, especially on the posterior surface (postmortem). The entire intestinal tract appears normal. The pancreas is pale-pinkish in color, quite firm and exhibits no noteworthy deviations from the normal. The mesenteric glands

are slightly enlarged, pinkish in color and somewhat softened. The retroperitoneal glands, especially those just above the promontory of the sacrum, are much enlarged, quite red in color, and very soft, and many of them being quite diffluent; indeed, such is the softening and diffluence that it is impossible to distinguish gland from gland; higher up glands may be differentiated, but all are enlarged, softened and red or pinkish in color. About the normal situation of the receptaculum chyli there are several enlarged glands scarcely to be differentiated from adjacent structures, but no receptaculum as a separate structure can be made out. Dissecting out the thoracic duct as high up as the clavicle no noteworthy changes can be recognized—in particular it is not enlarged or thickened. The brain and the spinal cord are not examined.

Anatomic Diagnosis. Sarcoma of the mesenteric, retroperitoneal and peribronchial glands; bilateral pleuritis with chyliform exudation; chyliform ascites; mitral stenosis and insufficiency; dilatation of the heart; slight sclerosis of the aorta; passive congestion, edema and cyanotic induration of the lungs; passive congestion of the liver, spleen and kidneys.

The following is the result of the microscopic examinations:

The enlarged mesenteric, retroperitoneal and peribronchial glands are the seat of a new-growth that has almost entirely replaced or destroyed the lymphadenoid tissue—to a varying degree, however, in different glands. The new-growth consists of elongated, for the most part, spindle-shaped cells, with ovoid, rather vesicular nuclei, that stain well. The cells are arranged parallel or almost parallel the one to the other, but they are collected in fasciculi that course in varying directions, whence longitudinal, transverse and oblique sections of the fasciculi are encountered. In many places the fasciculi seem limited to the sinuses, being apparently surrounded by a layer of flat endothelium; but in many places such arrangement and limitation are altogether wanting, and there is no appearance that warrants one in stating positively that the cells have been derived from proliferating endothelium. But little or no intercellular substance is apparent) by the ordinary methods of staining). Bloodvessels are comparatively few; those present have thin walls, mostly endothelium only, and they course amidst encircling fasciculi of tumor cells. Many of the retroperitoneal glands, especially those near the promontory of the sacrum, exhibit moderate necrosis. The other glands exhibit no retrograde alterations.

The pleura of the left lung is markedly thickened, the thickening involving the subendothelial connective tissue, the endothelium itself being wanting. This thickening consists of a highly vascularized fibrocellular tissue, the proportion of cells and fibrillar intercellular tissue varying in different regions. In general toward the free edge of the pleura the cellular collection consists of young fibroblasts and the ordinary round cells of inflammation; and the changes here merge rather rapidly into the more ordinary changes of fibrinous and fibrinopurulent exudation—a thick layer of which covers the pleura.

The pleura of the right lung exhibits the usual lesions of adhesive pleuritis with considerable round-cell infiltration. Throughout both lungs there is an unusual thickening of the alveolar walls, which, however, is not uniformly distributed; in regions where it is less marked there is considerable distention of the intra-alveolar capillaries, but where the thickening is more marked the capillary distention is obscured or absent. The thickening consists of a fibrocellular tissue rich in cells with elongated nuclei that stain well. Most of it appears to be white fibrous tissue, but there is a considerable proportion of elastic tissue. In some places the cellular new-growth is excessive and completely obliterates the lumen of several adjacent alveoli. One receives the impression that here and there there is an unusual proliferation from one side of the wall of the alveolus into its lumen; in other regions, doubtless because of transverse section of such a polypoid growth, the new tissue reposes in or fills an alveolus without manifesting attachment to its wall. In addition to this connective-tissue overgrowth, many of the alveoli are more or less filled with an exudation consisting of leukocytes, desquamated epithelium and a few erythrocytes. Many of the desquamated epithelial cells are excessively pigmented. This alveolar exudation is most marked just below the pleura of the left lung, where, together with the proliferation of the connective tissue of the alveolar walls, it gives rise to almost complete obliteration of the lumen of many alveoli.

The liver exhibits moderate dilatation of the central veins and adjacent capillaries, moderate pigmentation and slight atrophy of the regional liver cells. The spleen exhibits considerable thickening of the trabeculæ, and considerable pigmentation—partly free and partly within the cells of the pulp. The kidneys exhibit moderate passive congestion and slight degeneration of the epithelium of the convoluted tubules. The uterus exhibits a slight grade of hyperplastic glandular endometritis. Otherwise, there are no noteworthy microscopic alterations in the organs.

The fluid from the right pleural sac has a specific gravity of 1017. It contains 4 per cent. of albumin (Esbach). Microscopically there is considerable fibrin and a moderate number of cells, but none, or very few, of the fine granules observed in the fluid obtained by puncture from the left pleura during the life of the patient. A differential count of the cells reveals the following: lymphocytes, 58 per cent.; large mononuclear cells, 25 per cent.; polynuclear neutrophiles, 17 per cent. The lymphocytes and the polynuclear neutrophiles are readily identified. Some of the large mononuclear cells are doubtless degenerated lymphocytes, but the majority appear to be more or less degenerated and vacuolated endothelial cells.

The fluid obtained from the peritoneum has a specific gravity of 1016. It contains 3.5 per cent. of albumin (Esbach). Microscopically, there is a moderate number of cells and a large number of granules identical with those obtained from the left pleura. The granules are free and also contained

within certain of the cells. They stain blackish with osmic acid, and are dissolved with ether. A differential count of the cells reveals the following: lymphocytes, 70 per cent.; large mononuclear cells, 29 per cent.; polynuclear neutrophiles, 1 per cent. The large mononuclear cells are similar to those found in the fluid from the left pleura, though they differ among themselves. Many of them contain fine granules that are dissolved by ether, and stain black with osmic acid. They are doubtless desquamated endothelial cells.

Cultures from the right pleura and from the left pleura revealed staphylococcus pyogenes albus and aureus. Cultures from the peritoneal fluid revealed bacterium coli communis.

Within five hours of making the necropsy I inoculated three rabbits subcutaneously (in the William Pepper Laboratory of Clinical Medicine) with an emulsion of the softened retroperitoneal glands. One rabbit died the following day from peritonitis due to puncture of the intestine with the inoculating needle. The other two rabbits lived in excellent health, and were finally killed on April 6, 1905. No lesions were found at the necropsy.

SPHYGMOGRAMS FROM TWO CASES OF BRADYCARDIA.

By GEORGE DOCK, M.D.,
OF ANN ARBOR, MICH.

Comparatively few tracings have been published from cases of bradycardia. Even reports of such cases are not always convincing, because pains are not always taken to show that the heart beat is really infrequent. In a very recent report the pulse suddenly dropped to about half its former rate. As the heart beat is not described, nor the sounds mentioned, there is reason for thinking this was a case of alternating pulse (postoperative), a very different condition from bradycardia. Besides noting the rate of the heart beat, and the character of the sounds, it is essential to take tracings of the pulse, and also simultaneous tracings of the apex beat as well as the venous pulse. In the cases now reported it was not possible to get cardiograms or tracings of the venous pulse, but the sphygmograms of the radials seem of sufficient interest to excuse this and other unavoidable imperfections.

Case I. *Pulse about* 30 *for six years; in the last two years attacks of loss of consciousness; sudden death.*—C., farmer, aged sixty-three years. Health good up to four years ago, when there was an attack resembling influenza. At this time the pulse was found to be 28; the skin was cold. Various remedies were used, but the pulse never exceeded 30. The general health became fairly good, but shortness of breath remained. There was impotence for a time. Convulsions were not observed at any time.

I saw the patient once only, June 24, 1902, with his physician, Dr. James Hueston, of Ypsilanti. He was a man of large frame. The heart was slightly enlarged, the apex beat strong; there was a diastolic murmur over the mid-sternum. The peripheral arteries were only moderately sclerotic. Radial

pulse of medium size and fulness; wave well sustained but diastole long; 28; regular, following the heart beats with perfect regularity. There were no unusual pulsations in the neck. No capillary pulse. The other organs and the urine were negative. I made a diagnosis of probable Stokes-Adams' disease (the paroxysmal features of which, however, were not explained to the patient) and advised a course of atropine, partly in order to determine its effect on the pulse rate. This was given in full doses by Dr. Hueston, who never, however, found the pulse above 32.

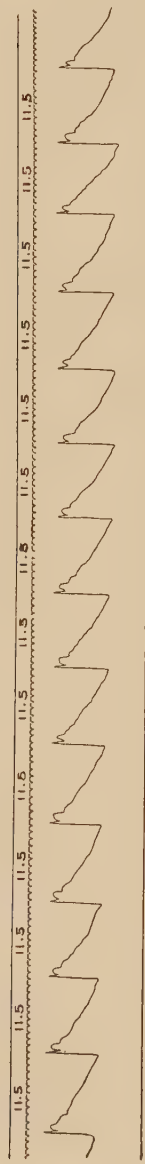
Soon after my examination the patient began to have attacks of loss of consciousness, falling suddenly at long intervals. The unconsciousness lasted three to four minutes. Some attacks followed exertion, others not. The final attack came on while picking fruit. The man fell down and was found almost at once to be dead. I often heard of him from Dr. Hueston in the mean time and he made many promises to come for examination, but never did, and as he lived some distance in the country I never found it possible to see him. I was fortunate enough to make an autopsy with Dr. Hueston. There was moderate arteriosclerosis, with very slight corresponding changes in the liver, kidneys and spleen. The kidneys were granular, but the microscopic alterations were relatively slight, with the exception of some minute old infarcts and recent hemorrhages. The vessels of the brain were not unusually sclerotic for a man of his age. The cerebellum, pons and medulla showed no macroscopic changes. Sections of the medulla at the level of the vagus centre show a slight diffuse increase of neuroglia, but the vessels and the nerve cells are not perceptibly altered.

The heart, weighing 500 grams, is slightly hypertrophied and shows only mild fibroid changes in the walls. The left auricle is thickened and fibroid, the right auricle shows slight separation of the muscular bundles. The auricular appendages are not affected. Microscopically the muscle fibres are well preserved, with no fragmentation. Both auriculoventricular orifices are slightly dilated. The aortic valves are slightly thickened and retracted. The aorta at the level of the coronaries is moderately sclerotic, but the coronaries from their orifices down show very little sclerosis without nodular thickening, retraction or dilatation. The sphygmogram (see Fig. 1) shows a shallow notch below the summit due to a slight exaggeration of the ventricular systolic wave, but the dicrotic wave is often very low. The chief feature is the slow rate, equal to 26.5 beats per minute, with a great regularity in the duration of each pulsation (11.5 fifths of a second), as well as in the height of the stroke. Several long tracings were taken, and all show the same details.

Case II. *Dyspnea, pain, palpitation of the heart; bradycardia* (15 *to* 30) *and arrhythmia.*—A. D., farmer, aged sixty years, seen with Dr. J. L. Ramsdell, of Albion, March 19, 1904. The patient was strong and muscular, and never ill until about one year before. He then began to have dyspnea on exertion, very slight pain, palpitation of the heart; no anginal symptoms.

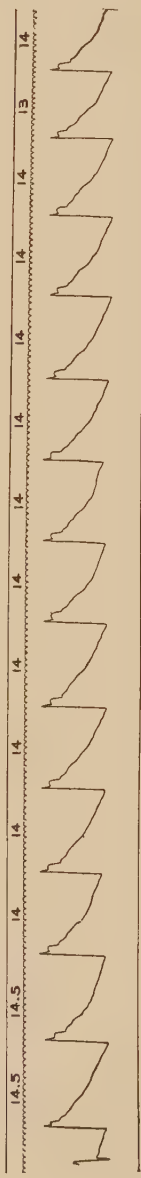
Dr. Ramsdell saw the patient four days before my visit and found the pulse 25. He then gave strychnin. A few hours before I saw the patient Dr. Ramsdell found a rate of 15.

FIG. 1



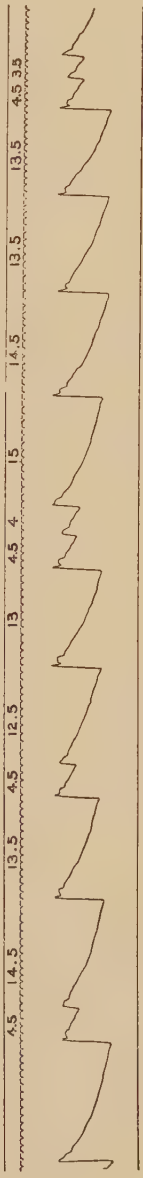
The time shown in one-fifth seconds; the figures above the tracings indicate the length of the pulse in this same fraction.

FIG. 2



The time shown in one-fifth seconds; the figures above the tracings indicate the length of the pulse in this same fraction.

FIG. 3



The time shown in one-fifth seconds; the figures above the tracings indicate the length of the pulse in this same fraction.

I found the patient spare, well preserved, but arteriosclerotic-looking. I noted: "The apex beat is in the nipple line, in the fifth intercostal space. Dulness begins in the third interspace, extends to the nipple line, on the sixth rib, and to the left edge of the sternum. At the apex the sounds are weak and there is a short systolic murmur conducted about one inch in various directions. This is followed by a soft diastolic murmur. The action is irregular. Sometimes the beat is very slow but regular, sometimes one or two beats follow a stronger one, but without regularity. The radial artery is of moderate size, the vessel tortuous, irregularly thickened; the pulse of moderate size, irregular, 25 to the minute. Usually there is a long pause, sometimes the pulse is followed by two weaker beats in rapid succession corresponding exactly to the heart sounds. There is no venous pulse. Blood pressure (Riva-Rocci after Cook, 5 cm. band), 185. Extremities warm, no edema. Has had tendency to cold skin all winter. The urine is negative. There are no brain or eye symptoms."

The tracings taken at this time illustrate the cardiac and pulse rhythm. Usually there is slow pulse, with intervals of about three seconds. Without obvious cause this changes to a very irregular pulse, or sometimes a regular irregularity, with intervals of from less than one second to five seconds or more. Both of these are shown in the tracings (see Figs. 2, 3 and 4). The waves with short intervals are always weaker than the long ones. Sometimes two waves follow a long pause and then the second pause is shorter than the first, but followed by a higher wave.

I made a diagnosis of arteriosclerosis with myocardial degeneration, and advised treatment with nitroglycerin, atropin and strychnin. There was no distinct change in the subjective and general condition after that, and no notable increase of the pulse rate.

April 9th, Drs. R. S. Morris and C. E. Edmunds kindly saw the patient for me and made some observations. The general condition was about the same as before. "The apex beat $1\frac{1}{2}$ to 2 cm. wide in the fourth intercostal space outside the nipple line. Dulness from the third interspace to the nipple line and the left edge of the sternum. The first sound at the apex weak, accompanied by a soft short murmur, transmitted about one inch upward and to the left, also toward the base. The second sound at the apex is strong and clear. The diastolic pause is very long. At the second right interspace the sounds are almost inaudible, also at the level of the third costal cartilage over the sternum. In this area the systolic murmur can also be heard, and followed up to the right sternoclavicular articulation, but not to the left.

"The peripheral arteries show marked sclerosis. Radial pulse 24 at first, later 30, but regular. The blood pressure (Cook), 176; Erlanger, systolic 162, diastolic 105 to 110. One mg. of atropin was injected, but no change of the pulse rate followed. The patient had taken $\frac{1}{150}$ grain atropin t. i. d. The pupils were wide in the beginning of the examination and did not become larger in the subsequent forty-five minutes of observation."

Tracings taken at this time show (see Fig. 5) a pulse of almost perfect regularity beating at the rate of 24.4 per minute. The patient died a few

FIG. 4

The time shown in one-fifth seconds; the figures above the tracings indicate the length of the pulse in this same fraction.

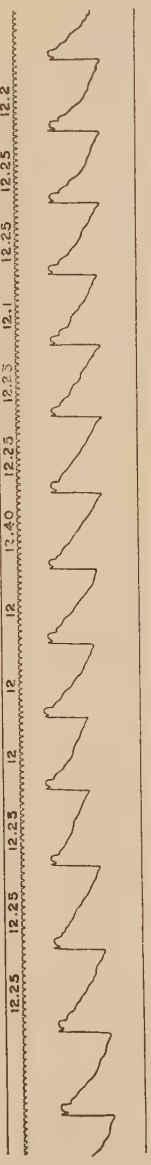


FIG. 5

The time shown in one-fifth seconds; the figures above the tracings indicate the length of the pulse in this same fraction.

weeks after this without any distinct change in his pulse conditions. An autopsy was not permitted.

These two cases have a relationship chiefly in the slow pulse. I think the first one should be classed among cases of Stokes-Adams' disease, though not a typical case. The slight retraction of the aortic valves does not seem to have been of much importance.

In the second case there were no Stokes-Adams symptoms, though these might have developed if the patient had lived longer. In this case the peripheral arteriosclerosis was more marked than that in any part of the body of Case I., but was no greater than occurs in many cases that never have bradycardia, Stokes-Adams symptoms or other unusual circulatory changes.

Both are cases of true bradycardia in that the heart beat had the same rate as the very infrequent pulse. Both failed to react to atropin in full doses. This makes unlikely a principal participation of the vagus center or trunk, which is also rendered unlikely in Case I. by the very long duration.

Aside from a vagus cause, the bradycardia might arise from: diminished automatic excitability; lowering of conductivity, or lessened contractility, or a combination of these.

Inasmuch as digitalis sometimes causes slow pulse by a toxic action on the heart muscle, I should say that in neither case was it given in such a dose as to produce an effect.

The regularity of the wave, the absence of signs of intermission in the tracing and of venous or cardiac signs on inspection and auscultation make it probable the slow pulse in Case I. was due to lowered automatic excitability. The same may be said of the regular curves in Case II. The irregular part in the latter case offers some interesting suggestions. There is a marked indication of "Luciani's periods" in the small waves, a disturbance of rhythm that occurs in certain disturbances of stimulus conduction in the heart muscle and capable of artificial production by asphyxia. In the patient, however, notwithstanding the great disturbance of the pulse at that time, there were no evidences of asphyxia, even with intervals of 3 to 5½ seconds between the

heart beats. This condition, however, probably did not continue very long.

Another possible explanation of the arrhythmia is that the long waves are due to intermission, the shorter ones showing the true rhythm; but the duration of the waves, as shown by the time marker, makes this unlikely, while the clinical evidence, again, was opposed to this view. The two long waves in Fig. 4 suggest missed beats, but in ausculting at other times with waves of five seconds' duration I could detect no contractions. The same sort of evidence negatives the supposition of "heart block," which might produce a tracing not unlike Fig. 3. A disturbance of contractility, or a negative inotropic action, might be supposed to be at work in both cases, but our knowledge of such disturbances in the human heart is too fragmentary at present to apply it to this case. Further experimental work and more thorough clinical investigation are much needed in this part of cardiac pathology.[1]

I should add that my friend and former colleague, Dr. A. R. Cushny, who has studied the tracings, also concludes that the chief element was diminution of automatic excitability in both cases.

[1] See especially "Arrhythmia of the Heart, a Physiological and Clinical Study," by Dr. K. F. Wenckebach, translated by Thos. Snowball, M.A., M.B., Edinburgh and London, 1904.

FURTHER OBSERVATIONS ON THE RELATION OF LESIONS OF THE GASSERIAN AND POSTERIOR ROOT GANGLIA TO HERPES, OCCURRING IN PNEUMONIA AND CEREBRO-SPINAL MENINGITIS.

By WILLIAM TRAVIS HOWARD, Jr., M.D.,
OF CLEVELAND.

(From the Pathological Laboratory, the Lakeside Hospital, Cleveland, Ohio.)

Introduction. At the meeting of the Association in 1902 I reported two cases of herpes, one of the lip and nose and the other of the trunk, occurring in acute croupous pneumonia, in both of which the sensory ganglia supplying the areas affected with herpes showed acute degenerative and exudative changes.

At this time I suggested that careful examination would disclose similar lesions in the sensory ganglia supplying areas affected with herpes, complicating other infectious diseases, especially cerebrospinal meningitis, typhoid fever and malaria.

Since then I have had opportunity to examine at autopsy two cases of cerebrospinal meningitis and one case of pneumonia with herpes. In all three cases definite lesions were found in the sensory ganglia supplying the herpetic areas.

In addition, I have seen in the wards of the Lakeside Hospital, in the service of my colleague, Dr. John H. Lowman, two unusual examples of facial herpes complicating non-fatal pneumonia.

REPORT OF CASES: HERPES COMPLICATING PNEUMONIA.

Case I. *Summary: Herpes of the skin of the right side of the nose, especially marked near the inner canthus of the right eye, occurring in a child with pneumonia complicating typhoid fever; degenerative and exudative changes in that portion of the right Gasserian ganglion, giving rise to the nerves supplying the*

skin of the upper portion of the nose; left Gasserian ganglion normal.—T. W., male, aged four years, was admitted on March 26, 1903, to the Lakeside Hospital, service of Dr. John H. Lowman, after an illness of thirteen days. He was drowsy and apathetic and breathed rapidly. Physical examination showed signs of consolidation of the upper lobe of the right lung. The spleen was enlarged. Widal reaction positive. There was a well-marked crop of herpes near the inner canthus of the right eye. On the morning of March 31st sloughing of the right cornea was recorded. Death occurred at 11.45 P.M., March 31, 1903.

Clinical Diagnosis. Typhoid fever, acute croupous pneumonia of the right lung, herpes of the right side of the nose, sloughing of the right cornea.

Anatomic Diagnosis. Typhoid fever (ileotyphus), hyperplasia of the mesenteric lymph nodes and the spleen, acute croupous pneumonia of the right lung (all three lobes), acute serofibrinous pleurisy, emphysema of the left lung, focal necrosis of the liver, cloudy swelling of the heart, liver and kidneys. Herpes of the right side of the nose, sloughing of the right cornea, congestion, hemorrhage and acute degenerative and interstitial inflammation of the right Gasserian ganglion.

Bacillus typhosus was isolated from the spleen and gall-bladder, and staphylococcus pyogenes aureus from the lungs, heart's blood and liver.

The autopsy was begun ten hours after death. The detailed description of the autopsy findings will be omitted. The Gasserian ganglion were of ordinary size. The veins about both were congested. The capsules and nerves of both were free from signs of inflammatory exudation. There was no meningitis.

Histologic Examination of the Gasserian Ganglia and the Fifth Nerve. Right Gasserian Ganglion: There was marked congestion of the veins along the convex border of the ganglion. Here, corresponding to a portion of the origin of the superior maxillary bundle of the fifth nerve, there was an area showing marked degeneration of the ganglion cells and infiltration of the interstitial tissue with leukocytes. The fifth nerve and its branches showed no degenerative or inflammatory changes. The *left Gasserian ganglion* and fifth nerve were normal.

CASE II. *Summary: Herpes of the right upper and lower lips, the right upper and lower eyelids and the right side of the neck, i. e., of the regions supplied by the right Gasserian and the right third cervical ganglia, occurring during an attack of acute croupous pneumonia, ending in recovery.*—Mrs. H. C., aged fifty-eight years, was admitted to the Lakeside Hospital, service of Dr. J. H. Lowman, on May 7, 1904, with the physical signs of acute croupous pneumonia of the lower lobe of the right lung, which later involved the entire lung. She was taken ill on May 3d, with a chill and pain in the right side of the chest. On admission there was an extensive crop of herpes involving both the upper and lower lips (most marked on the right side), and the right upper and lower lids of the right eye. There was conjunctivitis with granular lids on this side.

On the sixth day of her illness a crop of herpes appeared on the right side of the neck two inches below the angle of the jaw.

The patient recovered, so there was no opportunity to examine the sensory ganglia. The herpes ran the usual course of the so-called herpes zoster. In the light of our previous cases and of those of meningitis reported below, it is evident that the patient had extensive lesions of the right Gasserian and of the right third cervical posterior root ganglia.

Case III. *Summary: Herpes of the left lower eyelid occurring in the course of acute croupous pneumonia.*—In this man, also in the service of Dr. J. H. Lowman, there was herpes orbicularis occurring in a typical attack of acute croupous pneumonia, ending in recovery.

HERPES COMPLICATING CEREBROSPINAL MENINGITIS.

Case IV. *Summary: Epidemic cerebrospinal meningitis, with herpes of the right side of the face and neck, and of the left upper lip, and the vestibule of the nose and of the head and soft palate, regions supplied by both Gasserian and the third right cervical posterior root ganglia.*—D. L., male, aged twenty years, entered the Lakeside Hospital, service of Dr. H. H. Powell, October 27, 1904, complaining of severe pain in the head and the right side of the body. He had always been well until October 20th, when he was taken ill with chilly sensations and pain in the head and body.

Four days later he suffered severe burning pain in the right side of the neck. Later at this point a rash developed, followed by a large crop of herpetic vesicles. On admission there was marked rigidity of the neck, hyperesthesia and marked herpes, involving a large area on the right side of the neck below the angle of the jaw. Herpes later developed on the right cheek, near the ear. Kernig's sign was present. The diplococcus intracellularis meningitidis was isolated from fluid removed at lumbar puncture. Death occurred November 11, 1904.

Clinical Diagnosis. Epidemic cerebrospinal meningitis with facial and cervical herpes.

Autopsy. The autopsy was begun one hour after death.

The following is abstracted from the autopsy protocol: The body is that of a white male, 167 cm. long. There are extensive herpetic eruptions involving the right cheek just in front of the ear, the right side of the neck, the left upper lip and vestibule of the left nostril and the mucous membrane of the hard and soft palate on both sides. The eruption of the lip and nose is in the vesicular stage. That on the face and neck is covered with dry crusts. In the mouth the eruption is macular and pustular.

Nervous System. The dura and pia arachnoid are congested. Over the surfaces of the medulla and pons there is a thick fibrinopurulent exudate of gelatinous consistency. At the base of the brain and in the lateral ventricles there is a considerable amount of turbid fluid. The nerves at the base of the brain are enveloped in the exudate.

Gasserian Ganglia. Both are surrounded by a thick purulent exudate. The bloodvessels are congested.

Spinal Cord. The membranes of the cord are bathed in a turbid fluid. The pia arachnoid is covered with a fibrinopurulent exudate, which extends to

many of the nerve roots. The cord on section shows no appreciable changes. The third right cervical ganglion is larger than its fellows of the opposite side.

The other organs show no changes of present interest and their description is, therefore, omitted. The diplococcus intracellularis meningitidis was isolated in pure culture from the cerebrospinal exudate.

Microscopic Examination of Nervous System. The central part of the convex border of the ganglion, *i. e.*, that portion corresponding to the origin of the superior maxillary branch and possibly a portion of the inferior maxillary branch is the seat of extensive degeneration and destruction of ganglion cells, with leukocytic infiltration.

The affected ganglion cells are cloudy, stain poorly and are often hyaline. Some cells are swollen and others are shrunken. In those less affected the nuclei show no changes. In markedly degenerated cells, the nuclei may be eccentric and some stain diffusely. The leukocytic infiltration is most marked in the interstitial tissue, but some ganglion cell spaces contain leukocytes. The plexus of nerve fibres coming from this portion of the ganglion are surrounded with a fibrinopurulent exudate. Sections of the sensory root of the fifth nerve show no recognizable changes, when stained in either methylene blue and eosin or by Weigert's myelin sheath method.

Left Gasserian Ganglion and Fifth Nerve. In this ganglion similar changes are present and in the same portion of the ganglion as described in the right. The sensory root of the fifth nerve shows small scattered areas of cellular infiltration.

The Third Right and Left Cervical Ganglia and Posterior Root Nerves. The right ganglion is the seat of numerous small areas of ganglion cell degeneration and of interstitial and periganglion cell cellular infiltration. The changes are best marked at the distal end and at one side of the ganglion. The right posterior root is surrounded and infiltrated by large numbers of leukocytes. The left posterior root is similarly but less intensely affected. The left ganglion is normal.

Sections of the cord made at various levels show marked meningitis. The other ganglia are free from changes.

Anatomic Diagnosis. Acute epidemic cerebrospinal meningitis, due to diplococcus intracellularis meningitidis. Degenerative and exudative changes in both Gasserian and in the third right Gasserian ganglia, herpes of the hard and soft palate, the left upper lip, the vestibule of the nose, the right cheek and the right side of the neck.

In regard to the lesions in the third right cervical ganglion it is clear that the infection made its way along the posterior nerve roots. In the case of the Gasserian ganglia the route of the infection is not so clear, but it is evident that the inflammatory process is more marked in the nerve bundles about the ganglion than in the latter structure itself. It is to be noted that the distribution of the herpetic lesions correspond exactly with the ganglionic lesions.

Case V. *Summary: Trifacial neuralgia of the right side, suppuration of the sphenoidal sinuses; brain abscess and acute cerebrospinal meningitis, due to*

an actinomyces; herpes of the posterior and lateral cervical regions of the left side. —E. W., coachman, aged forty-six years, was admitted on February 11, 1905, to the Lakeside Hospital, service of Dr. J. H. Lowman, complaining of severe trifacial neuraligia of the right side. He denied having had any previous illness, except whooping-cough in childhood. He stated that he had been in good health until two weeks before admission, when his illness began with severe headache and backache. There was a slight chill, but no cough or other symptoms of disease of the respiratory tract. Ten days before admission he developed severe pain, paroxysmal in character, and tenderness on pressure of the right side of the face and head. Remedies applied in the hospital relieved this pain.

On February 13th, two days after admission, he developed symptoms pointing to brain abscess on the right side and to cerebrospinal meningitis. At lumbar puncture 70 c.c. of turbid fluid was obtained. From the fluid Dr. Louis W. Ladd isolated an actinomyces, which will be described in a future paper.

At this time there appeared well-marked herpes of the skin over the capital portion of the trapezius muscle and the angle of the scapula on the left side. There was no herpes elsewhere. Death occurred February 17, 1905.

Clinical Diagnosis. Abscess of the right side of the brain, cerebrospinal meningitis due to an actinomyces. Herpes of the neck.

Autopsy. The autopsy was begun a few hours after death. As this case will be reported in full in another paper, the present descriptions of the pathologic findings will be restricted to the lesions of the right fifth nerve and Gasserian ganglion and the third and fourth cervical ganglia and their roots.

Abstract of the Autopsy Protocol. The right Gasserian ganglion is of ordinary size. The sensory nerve of the fifth nerve is swollen and is marked by dark red streaks. The veins about the ganglia were markedly dilated.

Histologic Examination. Some of the veins of the capsule of the ganglion are found to be congested, but there is no hemorrhage. The ganglion cells stain normally, are not shrunken or invaded by cells. There is no infiltration of the interstitial tissue. In sections of the root of the fifth nerve stained with eosin and methylene blue, marked inflammatory lesions are found. The small veins and capillaries are congested and widely dilated. There are numerous areas of hemorrhage, which distort the nerve tissue. In many sections there are large accumulations of red blood corpuscles, leukocytes and large oval cells about the dilated bloodvessels. The large cells, which are most numerous are evidently proliferated connective-tissue cells. In sections stained by Weigert's myelin sheath method, there is marked breaking up and even disappearance of myelin sheaths about many of the fibres about the areas of hemorrhage and inflammation. The left Gasserian ganglion and fifth nerve show no pathologic changes.

Third Cervical Ganglia and Posterior Roots. The left ganglion is larger than its fellow of the opposite side. Histologically, the changes are marked. They consist in degenerated and necrotic changes in ganglion cells and in pro-

liferative and exudative changes in the interstitial tissue. The changes are confined largely to the proximal end and to one side of the ganglion. In the affected areas the capillaries and small veins are dilated, and here and there small areas of hemorrhage are seen. The degenerative changes of the ganglion cells vary from swelling and cloudiness, with failure of the granules to stain, to hyaline change and complete necrosis. Some cells show larger and smaller vacuoles. The necrotic cells are shrunken, and their nuclei do not stain. The nuclei of some of the degenerated cells stain diffusely. There is proliferation of the cells of the spaces about the ganglion cells. The latter are not, however, invaded by cells. The right ganglion is normal.

Posterior Nerve Root. Left. The inflammatory changes here are extreme. The nerve is surrounded by a thick fibrinopurulent exudate, and in many places there are larger and smaller areas of purulent exudation in the nerve itself. This is associated with both hemorrhages and proliferation of nerve cells. Similar but less intense changes are found in the right posterior root.

The Fourth Cervical Ganglia and Nerve Root. The left ganglia and its root show the same marked degenerative and inflammatory changes described in the third left. The right ganglion is normal, but its root shows marked perineuritis and endoneuritis. The other ganglia are normal.

Spinal Cord and Meninges. Sections of the cord and meninges cut at various levels show meningeal inflammation in varying degree. They are most marked at the level of the third and fourth cervical ganglia. Here the pia arachnoid is the seat of a marked fibrinopurulent exudation, which extends along the nerve roots on both sides. The polymorphonuclear neutrophilic leukocyte is the most common cell in the exudate, but large and small mononuclear leukocytes are also present. There are also numbers of large cells with single oval nuclei. A few long, thread-like organisms are found.

The cord shows no inflammatory changes, and its ganglion cells appear normal.

Anatomic Diagnosis. Actinomycotic abscess of the right occipital lobe rupturing into the right lateral ventricle. Suppurative inflammation of the sphenoidal sinuses, acute seropurulent cerebrospinal meningitis. Acute neuritis of the fifth nerve and of the third and fourth and other posterior nerve roots. Acute inflammation of the third and fourth posterior root ganglia of the left side; herpes of the left side of the back of the neck and of the left scapular region. Slight actinomycotic bronchopneumonia.

SUMMARY. A review of these cases shows a complete correspondence between the situation of the herpetic lesions and the ganglionic changes. In each case the distribution of the herpes was limited to areas of skin or mucous membrane supplied by the ganglia, which were the seat of the degenerative inflammatory lesions. In those cases with herpes of areas supplied by nerves from the Gasserian ganglion this relation is even more precise.

In Case I., for instance, with herpes on the nose near the inner canthus of the eye, the ganglionic lesion was limited to the point of origin of the superior maxillary nerve. In Case IV., with multiple herpetic lesions of the head (nose, upper lip, cheek, hard and soft palate), the lesions of the Gasserian ganglia again corresponded completely to the portion giving origin to the nerves supplying these parts. In Cases II. and III., though unsupported by anatomic examination, in view of the findings in the other cases, the inference that the herpes was associated with lesions of the Gasserian ganglia seems justified.

Case V. is of particular interest, for it demonstrates that, just as in spinal meningitis with involvement of the nerve roots, herpes does not occur unless the inflammatory changes extend to the ganglia; so in marked acute neuritis of the sensory root of the right fifth nerve, without appreciable changes in the Gasserian ganglion, herpes of the part supplied by this ganglion does not occur. In this case, under these conditions, there was severe trifacial neuralgia without herpes. Degenerative changes, with or without inflammatory lesions of the sensory ganglia, are therefore necessary for the excitation of the nervous impulses upon which the production of the herpetic lesions depend.

Cases IV. and V. also confirm the opinion expressed in my previous paper that the herpes of cerebrospinal meningitis is due to inflammatory lesions of the sensory ganglia.

The cases reported in this article furnish additional proof to support the position that the ordinary herpes zoster, as well as the herpes of pneumonia and cerebrospinal meningitis, is a pathologic condition dependent upon definite lesions of certain sensory ganglia, which may be caused by a variety of agents acting in different ways. The herpes is dependent upon the ganglionic lesions, and apparently does not vary with causes of the latter, whether they are due to embolism, thrombosis, hemorrhage, invasion by tumors, micro-organisms and other toxins or to other poisons. The ganglionic changes in the cases of herpes complicating pneumonia and cerebrospinal meningitis studied by me are identical with those described by Head and Campbell in their acute cases of so-called spontaneous herpes zoster. In the herpes of meningitis the ganglion changes are probably commonly due, as pointed out by Councilman, Mallory and Wright,

to an extension of the inflammatory process along the nerve roots to the ganglia. In pneumonia the materies morbi are apparently brought to the ganglia by the circulation.

References.

Howard. The Pathology of Labial and Nasal Herpes and of Herpes of the Body Occurring in Acute Croupous Pneumonia, and their Relation to the So-called Herpes Zoster. Transactions of the Association of American Physicians, 1902, and American Journal of the Medical Sciences, February, 1903.

Councilman, Mallory and Wright. Report of the Massachusetts State Board of Health, 1898.

Head and Campbell. The Pathology of Herpes Zoster and its Bearing on Sensory Localization. Brain: Part III., 1900.

THE FREQUENCY AND ETIOLOGY OF ACUTE NON-TUBERCULOUS PNEUMONIA IN A GENERAL HOSPITAL.

By WILLIAM TRAVIS HOWARD, Jr., M.D.
OF CLEVELAND.

(From the Pathological Laboratory, the Lakeside Hospital, Cleveland, Ohio.)

An examination of the index-catalogue of the autopsy records of the Pathological Laboratory of the Lakeside Hospital showed such frequent occurrence of acute non-tuberculous pneumonia at autopsy that I made a critical analysis of the relative frequency and the causes, both predisposing and determining, of this affection.

This hospital has about two hundred and twenty-five beds, divided into medical, surgical, gynecologic, and private ward services, all of which are active, and, in general, receive only acutely ill cases. The patients represent all classes of society. About two-thirds of the deaths come to autopsy.

This study is based upon a series of five hundred and fifty consecutive autopsies, which cover a period of about seven years. All doubtful cases and all cases of simple bronchitis are excluded. The diagnosis in every case is based upon microscopic as well as upon macroscopic examination. The autopsy technic is exhaustive, and the microscopic as well as the macroscopic appearances of the various organs are recorded in the protocols.

The routine bacteriologic investigation includes coverslip preparations from all exudates and plate, and other cultures from the heart, lungs, gall-bladder, liver, spleen, kidneys and exudates. The cultures are worked out with care.

The pneumonias are classified according to the usual custom into croupous or lobar and broncho or lobular.

The 550 consecutive autopsies furnish 195 instances of acute non-tuberculous pneumonia, an incidence of 35.45 per cent.

The cases of pneumonia are naturally grouped under several headings.

1. Primary pneumonia (for which the patients were brought to the hospital and were admitted as cases of pneumonia), 35, or 6.36 per cent. of the total number of autopsies.

(*a*) Acute croupous pneumonia, 31 cases.

(*b*) Acute bronchopneumonia, 4 cases.

2. Secondary pneumonia (developing in the hospital as a complication of some other disease for which the patient was admitted, as typhoid fever, appendicitis, nephritis, arteriosclerosis, injuries, etc. Many of these cases are "terminal infections"), 124 cases, or 29 per cent. of the autopsies.

(*a*) Acute croupous pneumonia, 36 cases.

(*b*) Acute bronchopneumonia, 124 cases.

1. The primary pneumonias present nothing of special interest.

Group (*a*). Primary croupous pneumonia, 31 cases, in which pneumococcus has occurred alone in 25 and with streptococcus in 2. Streptococcus was found alone in 1, and with B. mucosus capsulatus in 1. Staphylococcus pyogenes aureus was isolated in pure culture in 2. Pneumococcus was probably present in 4 cases in which we failed to find it, for, as is well known, this organism often fails to grow in cultures, and is not always found in coverslip preparations from exudates, from which cultures give positive results. Ten of the cases had arteriosclerosis and 10 nephritis. The former was the most marked lesion in 8 and the latter in 5 cases.

Group (*b*). Primary bronchopneumonia, 4 cases. Pneumococcus was found alone in 3 and streptococcus pyogenes alone in 1. All these cases occurred in young persons. One had chronic glomerulonephritis.

2. Secondary and often terminal pneumonias, 160 cases, 29 per cent. of the autopsies.

Group (*a*). Secondary croupous pneumonia, 36 cases, 6.5 per cent. of the whole number of autopsies. Pneumococcus occurred alone in 19 cases, with staphylococcus pyogenes aureus in 2, and with B. typhosus in 1. Streptococcus pyogenes was found alone in 2, staphylococcus pyogenes aureus alone in 4, and B. mucosus capsulatus in 3. B. coli occurred alone in 1. In five cases there is no record of the isolation of bacteria. It is quite probable that

pneumococcus was or had been present, and was overlooked for the reasons given above.

In this group of cases arteriosclerosis was present in 17 and chronic nephritis in 20.

Many of these cases were examples of terminal pneumonia developing in the course of serious and usually chronic visceral diseases. These were in the order of their importance: arteriosclerosis, 10; chronic nephritis, 3; cirrhosis of the liver, brain tumor, cerebral hemorrhage, epilepsy, gunshot wound of the brain, myocarditis, cholecystitis, chronic dysentery, carcinoma of the breast, 1 case each. There were 2 cases of carcinoma of the stomach, 1 of which was operated on. The cases of cholecystitis, gunshot wound of the brain and carcinoma of the breast were the only other of these cases undergoing operation. Of the remaining 13 cases there were 5 of typhoid fever (2 of which were operated on for perforation), 3 of appendicitis with peritonitis (all operated on), 1 of gunshot wound of the abdomen with peritonitis, 1 of puerperal infection, 1 of carbolic acid poisoning, and 2 of morphine poisoning.

Group (b). Secondary bronchopneumonia, 124 cases, or 22.5 per cent. of the autopsies. Cultures were positive in 120 cases.

Tables giving occurrence of bacteria in secondary bronchopneumonia:

TABLE I.—Giving Total Number of Cases in which the Various Bacteria were Present.

	Cases.
Pneumococcus	25
Staphylococcus	30
Streptococcus	23
B. mucosus capsulatus.	35
B. coli	16
B. typhosus	2
B. influenzæ	2
B. diphtheriæ	1
	134

TABLE II.—Showing Occurrence of Pneumococcus.

	Cases.
Pneumococcus alone	16
Pneumococcus and streptococcus	2
Pneumococcus and staphylococcus	1
Pneumococcus, streptococcus and staphylococcus	1
Pneumococcus, streptococcus and B. mucosus capsulatus	2
Pneumococcus and B. coli	2
Pneumococcus and B. influenzæ	1
	25

TABLE III.—Showing Occurrence of Staphylococcus Pyogenes Aureus.

	Cases.
Staphylococcus alone	18
Staphylococcus and streptococcus	5
Staphylococcus and pneumococcus	1
Staphylococcus, pneumococcus and B. typhosus	1
Staphylococcus and B coli	2
Staphylococcus and B. mucosus capsulatus	1
Staphylococcus and pneumococcus	1
	29

TABLE IV.—Showing Occurrence of Streptococcus Pyogenes.

	Cases.
Streptococcus alone in	13
Streptococcus and staphylococcus	5
Streptococcus, staphylococcus and B. typhosus	1
Streptococcus and B. coli	1
Streptococcus and pneumococcus	2
Streptococcus and B. mucosus capsulatus	1
	23

TABLE V.—Showing Occurrence of B. Mucosus Capsulatus.

	Cases.
B. mucosus capsulatus alone in	30
B. mucosus capsulatus and pneumococcus and streptococcus	2
B. mucosus capsulatus and staphylococcus	2
B. mucosus capsulatus and streptococcus	1
	35

TABLE VI.—Showing Occurrence of B. Coli.

	Cases.
B. coli alone	11
B. coli and streptococcus	1
B. coli and pneumococcus	2
B. coli and staphylococcus	2
	16

TABLE VII.—Showing Occurrence of Other Organisms.

	Cases.
B. influenzæ alone in	1
B. influenzæ and pneumococcus	1
B. typhosus alone	1
B. typhosus streptococcus and staphylococcus	1
B. diphtheriæ alone	1
	5

It is difficult to estimate the importance to be given to B. coli as a cause of pneumonia. It was the only organism found in 11 cases. It is probable that in at least some of these cases one or more other organisms may have been present and overlooked. It is interesting to observe, however, that of these 11 cases the primary disease was intestinal obstruction in 2, typhoid fever with perforative peritonitis in 1, and cholecystitis in 3. There was peritonitis in 9 of the 11 cases.

Of far greater interest, however, is the analysis of the primary diseases to which this series of bronchopneumonia was secondary.

The following tables give the incidence of bronchopneumonia in connection with various diseases:

TABLE VIII.—Acute Infections.

	Cases.
Typhoid fever	22
Meningitis	5
Phlegmon of subcutaneous tissues	5
Diphtheria	4
Acute endometritis (after abortion)	5
Umbilical infections	3
Pertussis	2
Empyema	3
Purpura hemorrhagica	1
Enterocolitis	2
Tetanus	1
Pemphigus	1
Appendicitis	2
	56

TABLE IX.—Non-inflammatory Affections of the Nervous System.

	Cases.
Injury to the brain (fracture of skull)	3
Injury to the cord (fracture of vertebræ)	2
Cerebral hemorrhage	2
Cerebral tumor	2
	9

TABLE X.—Diseases of the Liver and Biliary System.

	Cases.
Cirrhosis	2
Acute yellow atrophy	1
Abscess	1
Cholecystitis (abscess of liver in one case)	4
Dilatation of biliary passages and obstructive jaundice	4
	12

TABLE XI.—Certain Diseases of the Intestines.

	Cases.
Ulcers of the colon	1
Strangulated hernia	1
Intestinal obstruction (all had peritonitis at operation)	4
	6

TABLE XII.—Other Affections.

	Cases.
Arteriosclerosis (the most marked chronic lesion) in	12
Chronic nephritis (the most marked chronic lesion) in	3
Morphin poisoning	3
Carbolic acid poisoning	1
Thrombosis of large veins	2
Diabetic gangrene (amputation)	1
Extirpation of spleen (after injury)	1
Multiple fractures	2
Carcinoma of esophagus (rupture into trachea)	1
Tubo-ovarian abscess (chronic)	3
Pyonephrosis (death eleven days after suprapubic cystotomy)	1
Cardiac disease	8
	38

In the following cases bronchopneumonia developed after operation in individuals who had no apparent previous focus of infection:

TABLE XIII.

	Cases.
Gastroenterostomy	1
Carcinoma of neck (tracheotomy)	1
Carcinoma ovarii	1
	3

SUMMARY. It will be noted that 76, or about 61 per cent., of these cases occurred in individuals with acute infectious processes. Of the 43 autopsies on typhoid fever cases in this series 22 had bronchopneumonia and 5 croupous pneumonia. Of 81 cases of peritonitis from all causes 36, or 44.4 per cent., had pneumonia. A study of these cases does not indicate that operation in peritonitis increases the incidence of pneumonia. This point, however, needs further study. All the cases of diphtheria coming to autopsy had pneumonia. There were no autopsies in cases of scarlatina, measles or variola.

Individuals with chronic nephritis and arteriosclerosis are apparently more likely to have croupous than bronchopneumonia as a terminal infection. Thus, of 36 cases of secondary croupous pneumonia arteriosclerosis was the most marked chronic lesion in 10 and chronic nephritis in 3, while of 124 cases of secondary bronchopneumonia arteriosclerosis was the most marked lesion in 12 and chronic nephritis in 3.

It is of interest that B. typhosus was obtained from the exudate of 2 cases of bronchopneumonia and in 1 of croupous pneumonia in typhoid fever. It is doubtful, of course, if it held any etiological relation to the pneumonia, as it is commonly present in the blood in typhoid fever, and the typhoid bacilli present in the cultures from the lungs may have come from the pulmonary bloodvessels. Of the 21 cases of appendicitis coming to autopsy only 5 showed pneumonia, 3 croupous and 2 bronchopneumonia.

In the secondary pneumonias associated with acute infectious processes it is not always possible to determine whether the organisms reach the lung by inspiration or by the blood. Those associated with streptococcus infections and many of the staphylococcus and colon bacillus infections, especially cases of septic endo-

metritis, peritonitis and wound infections, are commonly embolic, while those due to pneumococcus and B. mucosus capsulatus are probably, in most cases, at least, examples of inhalation pneumonia. The pneumonias of typhoid fever are commonly inhalation pneumonias and are caused by a variety of organisms. In the croupous pneumonia of typhoid fever pneumococcus occurred in 4 out of 5 cases, in 2 alone, in 1 with B. typhosus and in 1 with staphylococcus and streptococcus. In the bronchopneumonias of typhoid fever the bacteria found were:

	Cases.
B. mucosus capsulatus alone in	9
B. mucosus capsulatus pneumococcus and streptococcus	1
Pneumococcus alone	1
Pneumococcus and streptococcus	1
Pneumococcus and B. coli	1
B. typhosus alone	1
B. typhosus streptococcus and staphylococcus	1
Streptococcus and staphylococcus	1
Undetermined	6
	22

In many of the secondary cases the areas of pneumonia were not extensive. This was especially true of the bronchopneumonias in which the process would often have been overlooked but for routine microscopic examination of the lungs. Since over 50 per cent. of our autopsies on typhoid fever cases showed pneumonia, it would be of interest to know the proportion of cases of this disease which have pneumonia and recover.

The clinical diagnosis of pneumonia was not made in many of the secondary or terminal cases. This is readily explained by the occurrence of the pneumonic process in patients so seriously ill with some primary disease that the disturbance entailed by a careful physical examination of the chest was not justified. It is evident that in a considerable number of these cases the complicating pneumonia had little influence upon the lethal issue, occurring as it did during the last hours of individuals destined to die of the primary disease for which they entered the hospital. In another class of cases, however, it is clear that the complicating pneumonia turned the scale and carried off patients who would otherwise have recovered, or, in chronic diseases, have improved.

In some of the cases there was general infection with pyogenic

organisms, which probably played a more serious part than the pulmonary affection. There are in the records, however, a considerable number of cases of chronic visceral disease, arteriosclerosis and chronic nephritis especially, with terminal general infections without pneumonia, which are not included in the present paper.

SOME CONSIDERATIONS ON PROTEID DIET:

WITH ESPECIAL REFERENCE TO ITS CONTENTS IN AMIDE-NITROGEN, MELANOIDIN-NITROGEN, DIAMINO-NITROGEN AND MONAMINO-NITROGEN.

By LEWELLYS F. BARKER, M.D.,

AND

B. A. COHOE, M.D.,

OF CHICAGO.

It is matter of common experience that a given individual may exhibit a variable tolerance for different kinds of proteid food; one may "agree" with him, while another "disagrees." The importance of a search for chemical differences in the foodstuffs, which may be responsible for such differences, is clear. Thus far but little has been done in this direction except (1) the simple determinations of total nitrogen and of elementary percentage composition which have been made;[1] (2) the interesting studies of Hall and of Burian and Hall[2] upon the purin-holding of the

[1] Some elementary meat analyses of various investigators.

	C.	H.	N.	O. and S.		Ash.
Ox flesh:						
(Stohman and Langheim)	49.25	6.91	15.49	23.03		5.32
(Rubner)	50.46	7.6	15.4	20.97		5.5
(Argutinsky)	49.59	6.91	15.31	22.95		5.24
Neck (young ox) (Koehler)	52.84	7.23	16.41	22.98	0.54	
Sirloin (young ox) (Koehler)	52.93	7.12	16.51	22.98	0.46	
Sirloin (cow) (Koehler)	52.22	7.19	16.59	23.42	0.58	
Pork (Koehler)	52.94	7.16	16.51	22.84	0.55	
Mutton (Koehler)	52.69	7.33	16.23	23.09	0.66	
Chicken (Koehler)	52.57	7.10	16.61	23.21	0.51	

[2] Die Bestimmung der Purinstoffe in tierischen Organen mittels der Methode der korrigierten Werthes, Ztschr. f. physiol. Chem., 1903, Bd. xxxviii., s. 336.

various meats,[1] and (3) the studies of v. Fürth and others upon the complex albumin bodies of muscles.

The object of the research here to be recorded has been to determine comparatively the distribution of the various forms of nitrogen compounds in a series of meats which are ordinarily used as foods. It is well known that proteid substances break down on hydrolysis into a whole series of decomposition products, chief among which are (1) a series of diamino acids, such as arginin, lysin, histidin, and cystin; (2) a series of monamino acids, monobasic or dibasic, such as glycocoll, alanin, amino-valerianic acid, leucin, tyrosin, aspartic acid, glutaminic acid, phenylalanin, tryptophan, prolin, oxyprolin and serin, and (3) ammonia.[2] These primary cleavage products of albumins are

[1] The results of investigations by Schur and Hall's method yield the following figures:

Substance:	Total purin nitrogen in moist organ.
Horse flesh	0.055 per cent.
Beef	0.062 "
Veal	0.071 "
Thymus (calf)	0.455 "
Pancreas (pig)	0.123 "
Pancreas (beef)	0.183 "

The fact is emphasized that different parts of the body give a different purin-nitrogen content. The neck, cited as an example, is poor in purin. According to the investigations of Hall:

	Purin-nitrogen.
Neck piece of calf gave	0.030 per cent.
Loin of calf gave	0.071 "
Neck piece of pork gave	0.023 "
Loin of pork gave	0.048 "

[2] *Monamino Acids met with in Albumins.*

Glycocoll (Amino-acetic acid $CH_2(NH_2).COOH$.

Alanin. (α-amino-propionic acid) $CH_3CH(NH_2).COOH$.

Leucin. (Amino-caproic acid or α-amino isobutyl-acetic acid) $(CH_3)_2.CH.CH_2.CH(NH_2).COOH$.

Phenylalanin (Phenyl-amino-propionic acid) $C_6H_5.CH_2.CH(NH_2).COOH$.

Prolin. (α-pyrrolidin-carbonic acid) $C_5H_9NO_2$.

Glutaminic acid (α-amino-*n*-glutaric acid) $CH_2\begin{cases}CH(NH_2).COOH.\\CH_2.COOH.\end{cases}$

Aspartic acid (α-amino-succinic acid) $COOH.CH_2.CH(NH_2).COOH$.

Serin (α-amino-β-oxypropionic acid) $CH_2(OH).CH(NH_2).COOH$.

Oxy-α-pyrrolidin-carbonic acid). $C_5H_9NO_3$.

Tyrosin (p-oxyphenyl-α-aminopropionic acid) $C_6H_4(OH).CH_2.CH(NH_2).COOH$.

Tryptophan (Skatol α-amino-acetic acid) $C_{11}H_{12}N_2O_2$.

Amino-valerianic acid. $C_5H_{11}NO_2$.

Diamino Acids met with in Albumins.

Arginin (Guanidin-α-amino-*n*-valerianic acid) $COOH.CH(NH_2).(CH_2)_3.NH\begin{cases}\diagdown CNH.\\\diagup NH_2\end{cases}$

Lysin (α-ε-amino-caproic acid) $NH_2.CH_2.(CH_2)_3.CH(NH_2).COOH$.

Histidin. $C_6H_9N_3O_2$.

Cystin. (α-diamino-β-dithiodilactylic acid) $COOH—CHNH_2—CH_2—S—S—CH_2—CH(NH_2)—COOH$.

believed to be united with one another in the form of long chains in the albumin molecule. Individual albumins are markedly different in their ultimate constitution. The albumins of muscle differ from those of milk; vegetable albumins differ from animal albumins. The variations are quantitative and qualitative. Thus, on the one hand the content in arginin of one albumin may be as much as 83 per cent., of another only 40 per cent., of a third only 20 per cent., and of a fourth less than 2 per cent. (Kossel); on the other hand, the variety of ultimate constituent amino-acids may vary greatly in the molecules of different kinds of albumin, the relatively simple protamins containing, perhaps, only four or five varieties, while it is known that serum albumin, for example, has as many as seventeen or eighteen different varieties of primary constituents.

A complete knowledge of the chemistry of meats will long be wanting to us, for it will necessitate, among other things (1), the determination of the different varieties of albumins in each meat; (2) the determination of the fragments into which the albumins of meats break down on digestion and on artificial hydrolysis, and (3) the exact way in which the ultimate constituent fragments are arranged in the molecular chains which the complex molecules represent. Inasmuch as cleavage appears to go far in ordinary digestion, absorption of cleavage products rather than of complex albumin bodies being probable, the second and third determinations referred to would appear *a priori* to be more immediately useful than the first, though a complete knowledge of (2) and (3) would, in all likelihood, give us a knowledge of (1).

Thanks to a method devised by Hausmann, modified and improved by Osborne and Harris and by Gümbel, we are able to make a preliminary survey of the holding of a given albumin (or of a mixture of albumins such as articles of proteid diet represent) in the different kinds of nitrogen bodies of which they are made up. It is possible to determine relatively easily and approximately accurately the proportions of the total nitrogen of an albumin (or of a meat) which are referable to (1) amide-nitrogen, (2) melanoidin-nitrogen, (3) diamino-nitrogen and (4) monamino-nitrogen, respectively. The results permit one to compare the holdings in various forms of nitrogen compounds of the different meats with one another, and with those of certain pure

albumin bodies which have been studied. It is this method which we have used. The task which we have set ourselves and its results are embodied in the following report.

We have undertaken the determination of the four forms of nitrogen above referred to in the following foods: pork chops, veal cutlets, sirloin, tenderloin and neck from the same animal (ox); liver (calf); thymus (calf); heart (calf); chicken (white meat from breast); fish (lake trout).

PREPARATION OF THE MATERIAL. After the removal of excess of fat the meat in each case was finely minced by means of a sausage-grinder. Dehydration was effected by placing the hash in 95 per cent. alcohol (changed several times) and later in absolute alcohol. The absolute alcohol, after two or three changes, was decanted off and ether was added. In order to remove the fat the material was placed in a large Soxhlet apparatus and extracted with ether for forty-eight hours, at the end of which time the ether washings were tested for a residue of fat. If any was found a longer extraction was made, until all traces of fat disappeared. The material was then dried and pulverized.

For each analysis the powder was dried to constant weight in a weighing tube, in a toluol oven, at 107° C.

METHOD OF ANALYSIS. The method employed was mainly that of Hausmann,[1] as modified by Gümbel[2] and Osborne and Harris.[3] The analysis comprises the following steps:

1. The cleavage of the albumin molecule by means of boiling concentrated hydrochloric acid.

2. The estimation of the so-called amide-nitrogen by distillation with magnesia.

3. The determination of the nitrogen occurring in the form of melanoidin or "humin bodies" carried down in the magnesia paste.

4. The precipitation of the filtrate from the magnesia paste with phosphotungstic acid and the estimation of the nitrogen (diamino or basic nitrogen) in the precipitate.

5. The determination of the nitrogen remaining in the filtrate

[1] Ueber die Vertheilung des Stickstoffs im Eiweissmolekül, Ztschr. f. physiol. Chem., 1899, Bd. xxvii., s. 95.

[2] Ibid., Beitrag z. chem. Physiol. u. Path., 1904, Hft.5 and 6, s. 297–312.

[3] Nitrogen in Protein Bodies, Journ. Amer. Chem. Soc., vol. xxv., No. 4.

not driven off by the magnesia nor precipitated by phosphotungstic acid (the monamino-nitrogen).

THE HYDROLYSIS. About 1 gram of the pulverized meat, dried at 107° until a constant weight was obtained, was boiled with 20 c.c. of concentrated hydrochloric acid (s. g. 1.20) for a period of eight to ten hours in a small flask provided with a reflux cooler. The solution was then slowly evaporated on the water-bath or *in vacuo* in order to remove a large excess of hydrochloric acid. About 5 to 10 c.c. of a residual solution of cleavage products of the proteid was thus obtained.

THE DETERMINATION OF THE AMIDE-NITROGEN. The solution of cleavage products was transferred to a distillation flask and about 400 c.c. of water added. Cream of magnesia, prepared by boiling a solution of magnesia oxid for several hours in order to remove every trace of ammonia, was added in slight but distinct excess of neutralization.

The distillation was carried on *in vacuo* at a temperature of 40° to 45° C. The ammonia driven off was received into a flask containing a known quantity of decinormal solution of sulphuric acid. From 250 to 300 c.c. was distilled over, usually requiring from three to five hours.

The receiving flask was kept cool by a stream of running water, or ice, in order to ensure condensation of the ammonia vapor, which might otherwise have been drawn off by the vacuum-pump, and caused a low figure for the amide-nitrogen.

If a low boiling point be not used the percentage obtained for the amide-nitrogen is apt to be too high, owing to the breaking up of some of the monamino acids upon boiling with magnesia at a high temperature. Embden has shown that cystin gives off ammonia on long boiling with magnesia. This source of error is avoided by boiling *in vacuo* at 40° to 42° C. (at which temperature cystin has been found to give off no ammonia [Gümbel]. No other cleavage product has been shown to liberate ammonia upon boiling with magnesia.

THE ESTIMATION OF THE MELANIN-NITROGEN (MELANOIDIN OF SCHMIEDEBERG.)—The "humin bodies" occur as black insoluble masses in the splitting of the proteid by hydrochloric acid. In the analysis they were determined (in the manner followed by Gümbel and Osborne and Harris simultaneously) by

determining the nitrogen remaining in the magnesia paste after filtration and complete outwashing of the paste with distilled water.

The paste was collected on a *Nutsche* (over nitrogen-free filter paper), and, after several washings with distilled water, the precipitate, together with the filter paper, was transferred to a Kjeldahl flask and digested with sulphuric acid, and the nitrogen determined according to the method of Kjeldahl. In Hausmann's method this fraction of nitrogen appeared in the diamino precipitate, and correspondingly increased the percentage of the diamino-nitrogen. (Our studies show that all, or nearly all, of the purin-nitrogen appears as "melanoidin-nitrogen" when the method is carried out as here outlined.)

THE DIAMINO-NITROGEN.—The filtrate, together with the washings from the magnesia paste, was concentrated *in vacuo* at 40° C. to about 100 c.c. The precipitation of the diamino acids was effected by means of an acidified solution of phosphotungstic acid of a strength suggested by Osborne and Harris, containing 20 grams of phosphotungstic acid and 5 grams of sulphuric acid per 100 c.c. About 30 c.c. of such a solution was necessary for the complete precipitation of the diamino acids in 1 gram of proteid. The precipitate was allowed to settle, and more phosphotungstic acid was added until a white precipitate no longer appeared in the supernatant fluid upon the addition of a few drops of the precipitant.

Upon standing, the precipitate, which at first is amorphous and flocculent, becomes granular.[1]

The precipitate was filtered on a *Nutsche* through nitrogen-free filter paper and washed with several washings, amounting in all to from 150 to 200 c.c. of a weak solution of phosphotungstic acid. This solution was made up of 2.5 grams phosphotungstic acid and 5 grams of sulphuric acid per 100 c.c.

The precipitate, along with the filter paper, was placed in a beaker and dissolved in a strong solution of sodium hydroxid (27 per cent.). In most cases 50 to 100 c.c. of such solution was used. The filter paper was removed by filtration, and the

[1] Gümbel states that crystallization of the diamino-phosphotungstates begins in from four to six hours. As a matter of routine it is found best to wait from twenty-four to forty-eight hours before filtering. The criterion in each case is the granular appearance of the precipitate.

solution of the phosphotungstates was diluted to a definite volume, usually 500 c.c., or in some cases to a litre. An aliquot part of this was taken and the nitrogen in it estimated according to Kjeldahl. From this the percentage of the diamino-nitrogen was determined. About 20 c.c. of sulphuric acid alone, or Kjeldahl acid, was used for digesting a volume of 200 c.c. of the solution. The oxidation was hastened toward the end by the addition of a few crystals of potassium permanganate.

In the concentration of the filtrate from the magnesia paste to 100 c.c. before precipitation with the phosphotungstic acid a slight brown precipitate frequently was present. This has been observed by Gümbel, who states that nitrogen could never be quantitatively demonstrated in it.

The sources of error in the estimation of the diamino fraction of the nitrogen are due on the one hand to the solubility of the phosphotungstates of the diamino acids (giving too low a percentage) and on the other to the tendency of the monamino acids to be precipitated by the phosphotungstic acid (yielding too high a percentage).

The diamino-phosphotungstates dissolve most readily in water, less easily in a solution of acidified phosphotungstic acid, and with still more difficulty if the precipitate be allowed to stand for twenty-four hours, until it becomes crystalline. The solubility is decreased by concentration of the solutions. Hausmann brought his solution after distilling off the ammonia to a volume of 70 to 80 c.c. Gümbel has determined that in a volume of 80 c.c. about 0.0035 gram of arginin (0.001 N) remains unprecipitated. This in an albumin molecule, with an arginin holding of 10 to 20 per cent., gives a loss of 1.8 to 3.5 per cent. This loss is increased by washing the precipitate, even when a dilute acidified phosphotungstic acid solution of the strength given above is used. For this reason as little as possible of the wash solution is used. Lysin is precipitated by phosphotungstic acid in a great dilution (over 1:6000). Histidin precipitates readily with phosphotungstic acid, but redissolves even in a slight excess of concentrated acid. In washing the diamino precipitate with dilute wash-phosphotungstic acid, if too concentrated an acid has been used in the precipitation, the histidin is reprecipitated in the filtrate and necessitates a second filtration; otherwise the histidin will be included in the

monamino fraction. Histidin is much less soluble in dilute solutions than are the corresponding precipitates of arginin and lysin. Hence, the rule laid down by Gümbel is to use an excess of phosphotungstic acid in precipitating, but not in too high a concentration, since otherwise histidin goes into solution. If a dilution of the fluid is made in which for one part of diamino-nitrogen there are 1000 to 1500 c.c. of solution, the conditions are most favorable for complete precipitation of the diamino acids. Under such conditions the error can be reduced to 5 to 10 per cent. of the total diamino-nitrogen.

The second source of error lies in the precipitation of the monamino acids with phosphotungstic acid. In very concentrated solutions, with the addition of strong acids monamino acids are precipitated with phosphotungstic acid. This does not take place with dilute solutions and with the addition of weak acids, such as are used in the experiment.

According to Winterstein, phenylalanin in a solution of 1 gram in 50 c.c. is no longer precipitated by phosphotungstic acid. Gümbel has shown that a .05 per cent. solution of hydrochloric acid of pure albumin cystin is not precipitated by phosphotungstic acid, even upon standing twenty-four hours. Osborne and Harris state that a careful examination of the phosphotungstic acid precipitates fails to reveal the presence of monamino acids, even when methods were used which would readily show the presence of very small amounts of leucin and tyrosin. They nevertheless conclude that monamino acids are to a slight extent carried down with the phosphotungstic acid precipitate.

Determination of the Monamino-nitrogen. The filtrate from precipitation of the phosphotungstates was made up to a definite volume (500 or 1000 c.c.). An aliquot portion of it (100 c.c. or 200 c.c.) was taken and digested with 30 c.c. of sulphuric acid, and an estimation of the nitrogen in it made according to Kjeldahl. On account of the high salt content of phosphotungstic acid in this solution the oxidation is extremely difficult and slow. (For this reason Osborne and Harris have suggested its estimation by subtracting the sum of the other forms of nitrogen from the total nitrogen of the proteid as determined by Kjeldahl.) If the excess of water be removed by slow evaporation, much of the bumping and possible loss of material is

avoided, after which the oxidation can be hastened by the occasional addition of a few crystals of potassium permanganate. This oxidation is slow, frequently requiring from twenty-four to thirty-six hours. The actual estimation of this fraction is important, since it serves as a control of the accuracy of the work by permitting a comparison of the sum of the percentages of the different fractions with the percentage of total nitrogen of the proteid in question. It will be noticed that the sums do not quite agree, and the defects of the method (or of technic) are thus made visible.

Determination of the Total Nitrogen. In each case an estimation of the total nitrogen was made according to the method of Kjeldahl.

It will be noted that the figures obtained refer in all cases to the nitrogen derived from the *article of food as a whole* (*extracted by alcohol and ether*).

Results. The results of the various determinations are presented in the following tables:

Table I.—Estimations of the Amide-nitrogen.

	Weight of dried material in grams.	Weight of nitrogen in the ammonia distilled with magnesia in grams.	Amide-nitrogen. Per cent.
Veal cutlets	1.1651	0.0119	1.02
Pork chops	0.6754	0.0071	1.06
Sirloin	0.7708	0.0044	1.04
Tenderloin	1.1256	0.0127	1.13
Neck	0.9843	0.0090	1.08
Heart	0.6641	0.0073	1.09
Liver	1.1438	0.0129	1.13
Thymus	0.8898	0.0107	1.19
Chicken	0.8848	0.0102	1.15
Fish	0.6612	0.0074	1.12

Table II.—Estimations of the Melanoidin-nitrogen.

	Weight of dried material used in grams.	Weight of nitrogen estimated by Kjeldahl.	Per cent.
Veal cutlets	1.3021	0.0033	0.25
Pork chops	0.6754	0.0019	0.29
Sirloin	0.7708	0.0029	0.37
Tenderloin	0.9931	0.0032	0.32
Neck	0.6950	0.0021	0.31
Heart	0.6641	0.0026	0.40
Liver	1.6539	0.0077	0.46
Thymus	0.8898	0.0032	0.36
Chicken	0.8848	0.0028	0.31
Fish	0.6612	0.0016	0.25

TABLE III.—ESTIMATIONS OF THE DIAMINO-NITROGEN.

	Weight of dried material used in grams.	Volume of the solution of the phosphotungstic acid phosphate in c.c.	Volume used for estimation cubic centimetres.	Weight of nitrogen obtained in aliquot part grams.	Per cent.
Veal cutlets	1.3021	1000	200	0.0097	3.74
Pork chops	0.6754	1000	200	0.0064	4.77
Sirloin	0 7708	500	200	0.0013	4.32
Tenderloin	0.9931	1000	200	0.0087	4.38
Neck	0.6950	1000	200	0.0057	4.13
Heart	0.6641	1000	200	0.0054	4.12
Liver	1.6539	1000	100	0.0084	5.09
Thymus	0.8898	1000	200	0.0113	6.39
Chicken	0.8848	500	200	0.0089	4.09
Fish	0.6612	500	200	0.0108	4.87

TABLE IV.—ESTIMATIONS OF THE MONAMINO-NITROGEN.

	Weight of dried material used in grams.	Volume of the solution of the phosphotungstic acid filtrate in c.c.	Volume used for estimation in c.c.	Weight of nitrogen obtained in aliquot part in grams.	Per cent.
Veal cutlets	1.1651	1000	100	0.0040	9.61
	1.3021	500	200	0 0517	9.63
Pork chops	0.6754	500	200	0.0275	10.17
Sirloin	0.7708	500	200	0.0297	9.65
Tenderloin	0.9931	500	200	0.0402	10.09
Neck	0.6950	500	200	0.0299	10.75
Heart	0.6641	500	200	0.0273	10.30
Liver	1.1438	1000	200	0.0228	10.00
	1.1438	1000	100	0.0116	10.19
	1.6539	1000	100	0.0157	9.50
Thymus	0.8898	500	200	0.0280	7.87
Chicken	0.8848	500	200	0.0372	10.51
Fish					10.69

DISTRIBUTION OF NITROGEN EXPRESSED IN TERMS OF THE WEIGHT.

		Amide-nitrogen per cent.	Melanoidin-nitrogen per cent.	Diamino-nitrogen per cent.	Monamino-nitrogen. per cent.	Sum of components.	Total nitrogen estimated by Kjeldahl.
	Veal cutlets	1.04	0.25	3.74	9.62	14.65	16.04
	Pork chops	1.06	0.29	4.94	10.17	16.46	15.44
Ox, same animal.	Sirloin	1.04	0.37	4.32	9.65	15.38	15.44
	Tenderloin	1.13	0.32	4.38	10.09	15.92	15.05
	Neck	1.08	0.31	4.13	10.75	16.27	15.49
	Heart (calf)	1.09	0.40	4.12	10.30	15.91	15.37
	Liver (calf)	1.13	0.46	5.09	9.89	16.57	15.16
	Thymus (calf)	1.19	0.36	6.36	7.87	15.78	15.72
	Chicken	1.15	0.31	4.09	10.51	16.06	15.85
	Fish	1.12	0.25	4.87	10.69	16.93	15.08

DISTRIBUTION OF NITROGEN EXPRESSED IN PERCENTAGES OF THE TOTAL NITROGEN.

		Amide-nitrogen.	Melanoidin-nitrogen.	Diamino-nitrogen.	Monamino-nitrogen.
	Veal cutlets	7.10	1.71	25.53	65.65
	Pork chops	6.43	1.76	30.01	61.78
Ox, same animal.	Sirloin	6.76	2.40	28.08	62.72
	Tenderloin	7 09	2.01	27.51	63.38
	Neck	6.65	1.91	25.46	65.98
	Heart (calf)	6.85	2.51	25.89	64.73
	Liver (calf)	6.82	2.78	30.72	59.68
	Thymus (calf)	7.54	2.28	40.31	49.87
	Chicken	7.16	1.93	25.46	65.44
	Fish	6.62	1.48	28.47	63.14

The agreements and the differences in the foregoing tables are sufficiently striking. How they are to be ultimately valued must be left to further investigations to determine. It is sufficient for the present that we are able to conclude that these various forms of nitrogen compounds are as evenly distributed in articles of proteid diet as they are seen to be, and that they also present in instances very distinct differences from one another, as the tables reveal.

DISCUSSION.

DR. VAUGHAN: I simply want to express my high appreciation of the work that has been done by Dr. Barker along this line. I have for some years held that the cell, whether it be a bacterial cell or a cell of the animal body, is a definite chemical compound, and I think soon I will have a supporter in Dr. Barker. If you take a cellular substance and purify it, extract from it everything that can be extracted with water, alcohol and ether, and then estimate the amount of amido, diamido and monoamido acids you will get exactly the same whether you use 0.1 or 5 per cent. acid. This suggests that the cell is a definite chemical molecule. Like Dr. Barker, I have no illusions. I do not believe that chemistry is going to solve the problem of the universe in a very short time, but it seems to me that if we regard the cell as a definite chemical compound, and impairment in cell function due to the introduction of some abnormal group into the cell or the abnormal arrangement of certain groups in the cell, then there is a possibility that man may some time in the dim and distant future be able by his researches to make internal medicine thoroughly scientific. I do not suppose we are going to do this in this generation or in the next, but it is more hopeful.

There is just one other thing I should like to refer to, that is we might use the diet that Dr. Barker has suggested here somewhat empirically in the

treatment of certain diseases. I have made a number of experiments during the last year in chronic parenchymatous nephritis with the different proteids, selecting proteids with reference to content of different amido groups. I am well aware that the data at my disposal is insufficient for any generalization as yet, but I am sure it makes a big difference in such a disease as chronic parenchymatous nephritis as to what proteids the individual is fed upon, in the amount of albumin excreted and the general condition of the patient is much better on certain proteids than it is upon others.

THE USE OF NUX VOMICA IN HYPERCHLORHYDRIA.

By J. H. MUSSER, M.D.,
OF PHILADELPHIA.

In 1885 the writer presented to the Philadelphia County Medical Society (*Therapeutic Gazette*, January, 1886) a communication on the use of ascending doses of nux vomica in various states. He pointed out that the value of nux vomica as a remedial agent was increased by the recognition that larger doses than usually prescribed could be borne, that a better effect could be produced by increasing the amount to be administered from a minimum dose to one which produces a physiologic effect, that such effect was more readily induced in old subjects and that a tolerance of the drug was soon established, so that from time to time it had to be given in increased amounts. In short, that the first dose should be fifteen drops t. i. d., and that every three days five drops should be added until a physiologic effect is produced, as headache, slight "swimming in the head" or vertigo, or perhaps muscular rigidity. When the patient is seen daily the drug could be pushed to the extent indicated. Practically, it was found that thirty to fifty drops was the average amount an old subject—*i. e.*, one after fifty—could take, and forty to eighty the dose the young adult could take. It must be borne in mind that the initial dose must be small, and that ascending doses, to tolerance, bring about the best results.

It was further pointed out that the drug was most useful in asthenic and atonic cases, whatsoever the nature of the ailment. The underfed subject who was under weight and suffered from the great group of fatigue symptoms, local and general, singly or combined, was likely to be relieved by this

remedy administered in the manner suggested. An example of the local effect of the remedy is seen in cases of eye-strain due to muscular insufficiency, as pointed out recently by de Schweinitz in his usual graphic manner. Whenever there is found a local disorder in the cardiovascular system, the gastrointestinal tract, or other portion of the economy, similar to the asthenic state of the eye muscle, nux vomica could be relied upon.

It is to a different local disorder, and one the relief of which at first sight may seem paradoxic, we wish to call attention—*i. e.*, the use of nux vomica in ascending doses in hyperchlorhydria or hyperacidity. It is well known that bitters are contraindicated in this state; that sedation rather than stimulation is required. In many instances we have found that sedative measures did not relieve the symptoms. A close study of the groups showed that they belonged to the class that had for its foundation a pure neurosis. In short, the hyperchlorhydria was not the result of a local irritative lesion, but an expression of a gastric neurosis the persistence of which was due to a general atony, anemia or a general fatigue neurosis. It is obvious that tonic measures would be required. To this class belongs the hyperchlorhydria subject in whom there is no local cause for gastritis and no pronounced evidence of ulcer or gastritis. They bear all the stigmata of an exhaustion neurosis. They are usually thin and wan subjects. They may be hypochondriacal and are often melancholic. They may have suffered from uterine or ovarian disease; show signs of gastroenteroptosis, or have evidence of chronic cholecystitis with or without calculi, or of chronic appendicitis or some other infection. They are usually constipated. The heart is weak, the pulse small and feeble and the tension low. The urine is at times abundant, watery, and hence of low specific gravity, but generally is scanty and high-colored, of high specific gravity and contains a faint trace of albumin and a few casts.

The class of cases outlined usually respond to ascending doses of nux vomica, and the symptoms of hyperacidity rapidly and often permanently disappear.

DISCUSSION.

Dr. Tyson: It has been a good many years since I listened to a paper on this same subject by Dr. Musser, in which he emphasized the same method of using the tincture of nux vomica. I adopted it in my own practice, following his suggestion, and I can confirm what he has said of its efficiency. I confess I have not advised it especially in cases of hyperchlorhydria. I prefer nux vomica to strychnin in many cases, the additional effect being probably due to its action on the mucous membrane of the stomach.

Dr. Stewart: To me this use of nux vomica is quite new, as I have been in the habit of avoiding nux vomica in this class of cases because of the presumed effect it has in increasing the flow of gastric juice. This I had gotten in the notion of because of the well-known effect of strychnin in this direction. I should like to ask Dr. Musser whether he gives nux vomica before or after meals, and what his maximum dose is?

Dr. Musser: I usually give the nux vomica before meals and the maximum dose varies with the individual. It is that very point that I attempt to determine by ascending doses. In no instance do I begin with a greater quantity than fifteen drops three times a day, and increase until an absolute physiologic effect is produced, or at least until fifty to sixty drops are reached. Formerly, I increased to massive doses, but sixty drops seem to be about all that is necessary if physiologic effect is not produced, as evidenced by slight stiffness of neck or a little vertigo—patients complain of being a little light-headed by smaller doses. If such effect is induced I reduce five or ten drops until the physiologic effect is not apparent. I continue at that proportion and increase it after the individual has lost the susceptibility to that dose.

STUDIES ON THE TOXICITY OF BILE.

II.

THE TOXIC EFFECTS OF BILE UPON THE CENTRAL NERVOUS SYSTEM, INCLUDING A STUDY OF THE ELIMINATION OF STRYCHNINE THROUGH BILE IN NEPHRECTOMIZED ANIMALS.

By S. J. MELTZER, M.D., and WILLIAM SALANT, M.D.

(From the Rockefeller Institute for Medical Research.)

---

1. The occurrence of severe nervous manifestations in the course of diseases in which icterus is a predominant symptom gave rise at an early period to experimental investigations of the effect of bile upon the animal organism. During the first part of the last century the methods employed in these investigations consisted, mainly, in intravenous injections of ox bile obtained from the gall-bladder. In most of these experiments the injections caused the death of the animal, which was then ascribed to the toxic effect of the bile. In the '40s of that century the view gained hold that the death following intravenous injections was not due to the toxicity of the bile, but to the impurities of the fluid used, which cause the formation of thrombi in the capillaries within the vital nerve centres; and Bouisson reported that animals which received filtered bile survived the intravenous injections without manifesting any important nervous symptoms. Such results could not have failed to exert a deciding influence upon the contemporary opinion, and we need not be surprised to find a man of the genius of Henle[1] making the statement that the widespread view of the toxicity of bile was an unwarranted prejudice. However,

[1] Handbuch der rationellen Pathologie, 1847.

after the discovery by Strecker[1] of the bile acids the numerous subsequent investigations were carried out almost exclusively with pure bile salts, and the question of the accidental causation of thrombosis no longer seriously entered into the discussion of the obtained results. The first investigation with bile salts was carried out in an extensive series by von Dusch.[2] Among the subsequent investigators we find such well-known names as Frerichs, Leyden, Kühne, Traube, Hoppe-Seyler, Landois and many others. The last investigation of our subject (the last, at least, as far as the effect upon the nervous system is concerned) was carried out some fourteen years ago by D. Rywosch,[3] under the direction of Kobert. It was a comprehensive, painstaking piece of work, which left its impress upon the subsequent writings on the subject of the toxicity of bile.

2. The present status of the views entertained concerning the toxicity of bile may be described as follows: All agree that bile is a very toxic substance. It hemolyzes red blood corpuscles; it can dissolve white blood corpuscles and other tissue cells; it retards and stops the heart beat; it lowers the blood pressure; it is capable of affecting the structure of nerve and muscle, etc. Regarding the effect upon the central nervous system, there is a unanimity of opinion that bile produces a depression. Most of the investigators described stupor and weakness of the animals as the predominant symptoms which follow the intravenous injection of bile salts in mammals, and coma and paralysis after the injections into the lymph sacs of frogs. A few investigators have also observed the occasional occurrence of convulsions. Von Dusch[4] describes three experiments in which the animals died in convulsions a few minutes after they received intravenous injections either of filtered bile or of sodium cholate. Röhrig[5] had similar results in two experiments, in which 7 c.c. of a 5 per cent. solution of sodium cholate was injected into the jugular vein. Leyden[6] also describes a few experiments in which convulsions appeared after injection of bile salts into the jugular vein. In one case the convulsions appeared immediately after injection of 1 c.c. of a

[1] Habilitationsschrift, Giessen, 1848.
[2] Habilitationsschrift, Leipzig, 1854.
[3] Inaugural Dissertation, Dorpat, 1891.
[4] Loc cit.
[5] Dissertation, Würzburg, 1863.
[6] Beiträge zur Pathologie des Icterus, Berlin, 1866.

10 per cent. solution of sodium glycocholate. In the vast literature on the studies of bile there are scattered records of a few more experiments in which convulsions figured as the result of the injection of bile. However, even Leyden, who, more than any other author, insisted upon the appearance of convulsions after intoxication with bile, states that, after all, it is a rare occurrence.

We[1] have stated in a previous paper that in most of these experiments the convulsions set in soon after the intravenous injection of bile or bile salts, and that they were simply terminal manifestations due to heart-failure, produced by too rapid injection of the solutions used in the experiments. In a few exceptional cases convulsions are recorded to have developed a day or two after subcutaneous or intraperitoneal injections. In such experiments, however, the bile, or the bile salts, produce extensive local necrosis, and the convulsions, which were seen days after the injection, were not necessarily nervous manifestations due to direct intoxication by bile. They might have been caused by absorption of toxic products from the necrotic areas or they might have been due to some terminal infections. In frogs the toxic symptoms appear soon enough after an injection of bile or bile salts into the lymph sacs, to be ascribed directly to intoxication by bile. Leyden,[2] Loewit[3] and Rywosch[4] experimented with frogs, and they all report that coma and paralysis are the only effects which they have observed after an injection of bile salts into the lymph sacs. Moreover, the last writer on the subject, Rywosch, asserts that in all of his extensive experiments, which included also mammals, he has never seen anything else but a depressing effect.

It was this last statement which caused the newer writers on the diseases of the liver to give up the older theory of cholæmia—namely, that it is caused by the absorption of bile. Cholæmia designates a complex of symptoms appearing in the course of acute yellow atrophy of the liver, or of any other form of *icterus gravis*. The symptoms are sometimes of a depressing character, like coma, etc., and sometimes they are manifestations of increased excitation; for instance, convulsions or excitation mania. On

[1] Meltzer and Salant. Journal of Experimental Medicine, 1905, vol. vii. p. 280.
[2] Loc cit.
[3] Zeitschrift für Heilkunde, 1881, ii., p. 459.
[4] Loc cit.

account of the occurrence of symptoms of the latter kind, Stadelman[1] and others insist that it could not be due to the absorption of bile, because, they argue, bile can cause only coma and similar symptoms of a depressing nature, but never convulsions. The recent observation by Biedl and Kraus,[2] that subdural injection of bile causes convulsions, can hardly be taken as a valid proof that bile contains a tetanizing element, since even minute doses of such substances as methylene blue, which, by intravenous injection, are almost harmless to the animal organism, can produce convulsions when injected subdurally or intracerebrally.[3] To repeat, briefly, bile, according to the present almost universally accepted view, contains a toxic element which is capable of producing nervous depression, coma and paralysis, but does not contain any element which can produce excitation and convulsions.

3. The experiments we have performed in this investigation consisted in animal injections of bile and bile salts. We have used most extensively rabbits' bile, but we have also made injections with ox bile and with bile from dogs and guinea-pigs. We also experimented with sodium glycocholate and sodium taurocholate. As to the animals in which the injections were made we have employed most exclusively frogs, the injections being made in the dorsal or ventral lymph sacs. There are good reasons for selecting frogs for these experiments. From what we have stated above it is evident that mammals are not very appropriate for these experiments. When the injections are made intravenously the rapid reactions which often follow are due to the effect of the bile upon the heart, and not to a primary effect upon the nervous system; when, on the other hand, the injections are made by other methods, the reactions sometimes set in so late as again to admit the doubt whether they are primary toxic effects of the bile. It is different with frogs. The reactions which follow the injections of bile into the lymph sacs set in early enough to be due directly to the intoxication with bile; nor can there be any suspicion that the nervous manifestations are secondary to some disturbances in the circulatory or respiratory systems.

[1] Ueber Icterus, Stuttgart, 1891.
[2] Centralbl. f. klin. Med., 1898, p. 1185, 19 Jahrgang.
[3] Bruno, Deutsche med. Woch., 1899, p. 369, 25 Jahrgang.

4. As the main title of our paper indicates, the chief work of this research was devoted to a study of the toxic effects of bile upon the central nervous system. This, however, was not the primary problem which started us on this long investigation. We started out in quest of a solution to a problem which presented itself to us in the course of our previous researches. Soon, however, we became confronted with the question of the normal toxicity of the bile. In taking up the new thread we arrived at results which shed new light on the new problem, assisting us at the same time in throwing some light on our original question; and herein will be found the reason for using, essentially, rabbits' bile and experimenting with frogs. In presenting our results we should traverse the tortuous path by which we gradually arrived at them. We shall, therefore, begin with a presentation of our original problem, which started us on this path. It was as follows:

5. It is an established fact that strychnine which is introduced into the body by any path leaves it again completely through the kidneys. The kidneys are the main eliminating organs for it. Now, we[1] have found that after double nephrectomy two or three times the fatal dose of strychnine can be gradually injected without causing any intoxication, provided each single quantity is less than the minimum dose and the intervals between the injections are not too short; in other words, after nephrectomy there is no cumulative effect of the strychnine in the blood. One of the possible explanations for this remarkable condition is the assumption that after nephrectomy the process of elimination is assumed by another organ. The gastrointestinal canal suggested itself to us,[2] but we failed to detect strychnine there. Later[3] it was found that with the methods at hand it is quite difficult to discover small doses of strychnine in the intestinal canal. In further pursuance of the hypothesis of vicariation we turned our attention to the bile through which, as is claimed, poisons are normally eliminated from the body. Our plan was to investigate whether after nephrectomy strychnine becomes eliminated through the bile. Our previous experiments were made on rabbits; we had,

[1] Meltzer and Salant, Journal of Experimental Medicine, 1901–1902, vol. iv. p. 107.
[2] Salant, American Medicine, 1902, vol. iv. p. 293.
[3] Salant, Journal of Medical Research, 1904, vol. xii. p. 41.

therefore, to repeat them again on the same animals; hence the preferred employment of rabbits' bile in this investigation. Furthermore, the chemical process of obtaining strychnine from bile is very tedious work, and it would become quite unmanageable if, as was our plan, many experiments were to be performed. We have therefore resorted to the employment of the biologic test—*i. e.*, the injection of the bile, which we expected to contain strychnine, into frogs, and to watch for the known strychnine symptoms. That is the way we came to use frogs and rabbits' bile in this research.

6. In attempting to solve the problem we had in hand we carried out several sets of experiments. In one series rabbits were nephrectomized and the common bile-duct ligated. After recovering from the operation the animals, received several subminimum doses of strychnine. These animals were studied in the first place with reference to the amount of strychnine they would stand without responding with a convulsion, and in the second place, after the death of these animals, the bile from the gall-bladder and from the dilated duct was tested for the presence of strychnine by injecting it into frogs. In another series of experiments a cannula was tied in the common duct of nephrectomized rabbits, and, after injecting subcutaneously subminimum doses of strychnine, the collected bile was tested on frogs. The following is a brief *résumé* of the results of these experiments:

7. Series I. *Both Kidneys Removed, the Common Bile-duct Ligated and Subsequently Subminimum Doses of Strychnine Injected at Varying Intervals.* This was carried out on seven rabbits. In four animals there were no signs of a cumulative effect, although the sum total of the several doses of strychnine in every animal exceeded by far the minimum fatal dose (about 0.6 mgr. per kilo.). One of these animals lived seventy-four hours, and received during that time nearly 3 mgr. per kilo. without the slightest show of convulsions, or even hyperæsthesia. It died under the symptoms of exhaustion.

The behavior of these four animals was exactly the same as that of nephrectomized rabbits without the ligation of the common duct.

Of the remaining animals, one received within twelve hours about 0.9 mgr. per kilo. without showing any effects. Three

hours later, however, when it again received about 0.2 mgr. per kilo., the animal had a tetanus and died in a few minutes. The course in this experiment did not differ materially from that which sometimes occurred in our previous experiments on nephrectomized animals without ligation of the duct, when they received strychnine in refractive doses.

The remaining two animals, however, died in violent convulsions two hours after receiving only 0.3 mgr. strychnine per kilo. This dose is, as a rule, not toxic even in normal animals.

These observations, then, did not permit positive conclusions one way or the other. In the majority of the animals the additional closing of the eliminating path through the bile did not increase in the slightest the cumulative effect of the poison within the blood, which would speak against the elimination of the strychnine through the bile; on the other hand, in two experiments the ligation of the bile-duct had rather a strikingly aggravating effect upon the injection of even a single subminimum dose of strychnine. Furthermore, we had to take into consideration that the absence of strychnine symptoms in the majority of these experiments could not be taken as an absolute proof for the absence of strychnine in the bile. It is possible that the refractive doses of the strychnine were indeed eliminated from the blood and accumulated largely in the bile within the gall-bladder, but through the abnormal state of the bladder under these conditions the strychnine was prevented from being reabsorbed into the circulation; hence, the absence of convulsions in the majority of the experiments. In this case, however, we would expect that the bile of these animals when injected into frogs would produce symptoms of strychnine poisoning. This was put to a test. From four of the rabbits of this series bile was obtained from the gall-bladder and the dilated-bile duct. The quantities were, of course, small, and only a few experiments were made. The few results were as follows:

1 c.c. of the bile injected into a medium-sized frog caused coma in one hour, and in a small frog $\frac{1}{2}$ c.c. caused complete coma and paralysis one-half hour after injection. As to the balance we can say, briefly, that none of the frogs which received smaller or larger doses of the bile from the rabbits of this series had convulsions or showed any hyperæsthesia.

These few observations, then, did not indicate that the bile contained strychnine, or, at least, not in such doses as to produce the characteristic symptoms in frogs.

8. At this stage we had to remember that the preceding experiments were capable only of providing a positive proof—*i. e.*, that if all the animals would have manifested strychnine poisoning, or if the bile of these animals would have contained strychnine, we would have had a positive proof that after nephrectomy strychnine is eliminated through the bile. However, the failure of these experiments to bring forward a positive proof could not be interpreted as a negative proof—*i. e.*, that the bile organs do not assume the function of elimination of strychnine after nephrectomy; because, just as we have assumed that after removal of the kidneys another organ, the liver, takes over the function of elimination, we may now assume again that after nephrectomy and ligation of the common duct still another organ or organs assumes the work of elimination of strychnine; hence, the failure of the above experiments to connect the bile with strychnine.

More satisfactory evidence in favor of or against that assumption we expected to obtain from the following set of experiments:

9. Series II. *Rabbits were Nephrectomized and a Cannula Fastened into the Bile-duct; the Animals then Received Strychnine in Subminimum Doses and the Collected Bile Was Injected into Frogs.* We made six such experiments. In five animals some bile was collected before the strychnine injections were instituted. This bile was also injected into frogs which served as control. All the frogs which received bile from the ante-strychnine period responded with coma, and all but one became paralyzed and died. None of the frogs showed tetanus, rigidity or convulsions, and all but one showed even no hyperæsthesia. One showed marked hyperæsthesia, but soon also passed into coma and paralysis.

The frogs which received the bile from the strychnine period offered a different picture. The bile from one rabbit which received within six hours 0.7 mgr. of strychnine nitrate produced in three frogs tetanus and death in twenty minutes. The bile from another rabbit which received 2 mgr. of strychnine in forty-eight hours produced tetanus in two frogs, marked hyperæsthesia in one, and had no effect in another—in the last

case with such a large dose as 3 c.c. of the bile. Two rabbits received about 0.3 mgr. of strychnine. The bile of one produced tetanus in one, marked hyperæsthesia in another, and coma and paralysis in a third frog. The bile of the other produced late rigidity and convulsions in one and coma in another frog. Of the remaining two rabbits one received 0.5 mgr. of strychnine in a single dose. The bile gave in one frog hyperæsthesia, which terminated in coma, and in the other it produced only coma. The same was the effect of the bile of the last rabbit, which received a single dose of strychnine. (The amount is not noted in the protocols.) The bile (strychnine period) from the rabbits of this series produced then distinct strychnine symptoms (hyperæsthesia, etc.) in nearly all the frogs, while even distinct tetanic attacks were produced by the bile of rabbits which received at least toxic doses. Comparing these results with those obtained with the bile from the ante-strychnine period of the same series, the conclusion seems to be justified that in these animals some of the strychnine, at least, was eliminated through the bile.

10. Some new questions now arose. In the first place, whether the presence of some strychnine in the bile of this series of animals is only a vicariation process; in other words, whether in normal animals which receive strychnine the bile does not also, as a rule, eliminate some of this poison. In the second place the question had to be studied whether the bile of nephrectomized animals, without receiving strychnine, does not eliminate from the body a tetanizing element of metabolic origin, and whether it might not have been the presence of such an element in the bile, and not that of strychnine, which caused the hyperæsthesia and convulsions in the last series of experiments. Both questions were tested by short series of experiments.

11. Series III. *Bile Collected from a Cannula in the Common Duct of Normal Rabbits Before and After the Injection of Strychnine and Tested on Frogs.* Only three such experiments were made. One animal received 0.9 mgr. of strychnine. 2 c.c. of the ante-strychnine bile gave coma, which developed gradually within one hour. 2 c.c. of the bile of the strychnine period gave marked hyperæsthesia, and the addition of 2 c.c. more of the bile brought out immediately a violent tetanus, which passed over rapidly into coma and paralysis.

In the second experiment the rabbit received 1 mgr. of strychnine. 2 c.c. of the ante-strychnine bile gave coma, as before, whereas the same amount of bile of the strychnine period gave pronounced hyperæsthesia, which, after an hour, passed over suddenly into coma. (The very brief period of convulsions might have been overlooked.) In both these experiments the urine collected after the administration of strychnine was also tested. It had almost no effect.

The third animal received 1.5 mgr. of strychnine. 2 c.c. of either bile (before and after strychnine injection) produced no effect. 3 c.c. of the bile of the strychnine period produced coma, while 3 c.c. of the bile of the ante-strychnine period produced rigidity of the frog. (The urine of this animal produced increased reflexes in frogs.)

Here we have two experiments in which the bile from non-nephrectomized rabbits after injection of strychnine produced marked hyperæsthesia, and even a convulsion, while in the third experiment the normal bile of the rabbit (before receiving strychnine) produced symptoms distinctly similar to those of strychnine poisoning.

12. Series IV. *Bile Collected from the Common Duct of Nephrectomized Rabbits and Tested on Frogs.* We had five such experiments. In one even 3 c.c. of the bile produced no effect upon the frogs, but 3.5 and 5 c.c. brought on prolonged tetanic attacks. In another experiment 3 c.c. had no effect and 5 c.c. produced hyperæsthesia, but neither convulsions nor coma. In a third experiment 5 c.c. brought on hyperæsthesia and stupor. Of the bile of the fourth experiment 3 c.c. had no effect, but 5 c.c. brought on coma and paralysis. Finally, in the fifth experiment already 2 c.c. of the bile produced coma and paralysis. In this series, again without any strychnine, marked hyperæsthesia was a frequent phenomenon, and there were also very distinct tetanic attacks. On the other hand, coma and paralysis were seen only in two cases, and in one case only after injecting such a large dose as 5 c.c. of the bile.

13. A remarkable feature of this series was that in nearly all of the experiments such large doses of bile as 3 c.c. should have produced no effect at all. The control bile of all the previous experiments (except one) produced with 2 c.c., and sometimes

even with 1 c.c., distinct coma and paralysis. The ante-strychnine bile in the second series was also obtained from nephrectomized rabbits, and is therefore comparable with the bile of the last series in every respect except one—that it was obtained at the very beginning of the flow of bile from the cannula. This latter might, indeed, be an important feature, and might, perhaps, explain the absence of hyperæsthetic and convulsive effects in the bile of the ante-strychnine period of that (second) series. We may, perhaps, assume, indeed, that the hypothetic tetanic element which normally is eliminated through the urine, and which, after nephrectomy, finds its way out of the body through the bile, appears there in effective doses only some time after nephrectomy, the vicariation developing only gradually. The bile of the fourth series was collected during a long period, sometimes extending over two days and longer after nephrectomy, whereas the bile of the ante-strychnine period of the second series was collected only an hour or two immediately following the nephrectomy. Hence, the absence of a tetanic element in this bile and its frequent occurrence in the bile of the fourth series.

However, while this might explain satisfactorily the occurrence of hyperæsthesia and convulsions in the experiments with the bile of the fourth series, it does not explain the remarkable reduction of the toxicity. What factor could cause the surprising reductions of the elements producing coma and paralysis in the bile of the fourth series, so that even such quantities as 3 c.c. produced no effect?

A question arose now: Could the presence of a tetanic element in the bile, be it strychnine or be it some catabolic product, influence the activity of the elements of coma and paralysis, normally present in the bile, so as to neutralize to some degree the depressing effect?

14. However, before that question could be properly disposed of a more fundamental question confronted us and had to be studied. What is the actual effect of the bile collected for a longer period from the common duct of a normal animal? In the experiments of the preceding several series we did not yet deal with such bile. The control bile of the third series, which was such normal bile, was collected only for a short period, and soon after the operation (the introduction of the cannula into the

bile-duct), where also the possible after-effect of the anæsthesia has to come into consideration. Besides, even in this short series the results were not uniform. The control bile of the three experiments produced coma and paralysis in two and rigidity in one.

From the above-quoted literature we learned that the opinion is now generally held that bile produces coma and paralysis. As far as we know only three investigators experimented with frogs. Leyden made injections in three and Rywosch in four frogs. Loewit, who probably made many injections, gives only general conclusions. All the three investigators employed in their injections chiefly biliary salts, and when bile was used it was ox bile obtained from the gall-bladder. It is generally assumed that bile from the gall-bladder is more poisonous than that from the common duct. From all this it is evident that there was as yet no information whatsoever as to the behavior of bile collected from the common duct of normal rabbits. Such a study we have now carried out in a large number of experiments. In the following pages we shall report the general results. We shall also report briefly some results we obtained from experiments with stagnated bile—from the gall-bladder or from the dilated ligated duct of otherwise normal rabbits.

15. Series V. *Bile of Normal Rabbits.* (*a*) *Bile from the Gall-bladder or from the Dilated Ligated Duct.* We made only a moderate number of such experiments. The results were as follows: Such small quantities as 0.5 c.c. produced no immediate effect, but most of the animals were found dead the next day. 1 c.c. produced, as a rule, coma and paralysis an hour or two after injection. In two instances even 1.5 c.c. produced only a moderate effect, which set in late. (It seemed that injections into the ventral lymph sac brought out the effect more promptly than when the bile was injected into the dorsal lymph sac. Possibly the abdominal pressure in the normal posture acts like massage and hastens absorption.) In no case was any increase of reflexes or convulsions or rigidity observed.

16. (*b*) *Bile Collected from a Cannula in the Common Duct.* As a rule large quantities of bile were collected in this manner, sometimes more than 100 c.c., and thus experiments could be performed upon many frogs with the bile obtained from one

animal. The data which we give were gathered from experiments made with bile of nine different rabbits. In many of the numerous experiments the employment of the normal bile was a part in one or another experiment in which the injection of the normal bile served as a control for comparison with the effect of injection of bile of some other kind.

The chief result of this series is the assured fact that bile of some rabbits undoubtedly can produce distinct hyperæsthesia and tetanic attacks. Whether the bile is moderately or strongly toxic and whether the predominating toxic effect is depressing (coma and paralysis) or exciting (hyperæsthesia and convulsions) in character seemed to depend greatly upon the individuality of the animals. From our experience with the animals of this series, as well as from observations gained in the various series of experiments in this research, we believe to be justified in dividing the animals into three groups, according to the above-mentioned individuality.

The bile of one group of rabbits produced, essentially, coma and paralysis. In this case a quantity of 2 c.c. would, as a rule, produce coma and paralysis within a few hours after injection, and the larger the injected quantity the sooner the coma and paralysis would set in and the more complete they would be. Quantities less than 2, but above 1 c.c., produce during the first eight or ten hours of observation hardly perceptible symptoms, but the next day, or on the third day, the animals would be found dead. 1 c.c. of bile hardly had any effect. With the bile of these animals no hyperæsthesia or convulsions could be produced with any quantity. The quantities given here are, of course, subject to some variations. The principal point is that the bile of this group of animals produces only coma and paralysis, and never hyperæsthesia and convulsions.

17. From a second group of animals bile in quantities of 2 c.c., or even 2.5 c.c., would produce no effect, neither soon nor later. 3 c.c. of bile would cause more or less marked hyperæsthesia sooner or later after the injection, but the majority of the frogs would recover from the effects. Doses of 5 c.c. of this bile produced more or less distinct symptoms of coma and paralysis, and the larger the dose the more complete the symptoms would be and the sooner they would set in. The animals never survived

these symptoms. The main characteristic of the bile of this group is that the smaller dose produced hyperæsthesia and the larger dose produced coma and paralysis. Exceptionally, the coma would be ushered in by a very short convulsive attack. These attacks are very brief, and might easily be overlooked. Possibly they have indeed occurred more often than they were noticed by us.

18. The bile of the third group produced in doses of 2 or 3 c.c. mostly no perceptible effect. 3.5 c.c., and more, would produce marked hyperæsthesia, which would pass over into clonic or tonic convulsions. In some cases a violent tetanus would set in two or three hours after injection of the bile; in other cases the tetanic effect would not appear before the next day, sometimes only after prolonged handling of the frogs, and the tetanus would be of a pronounced toxic character, the animal remaining rigid uninterruptedly for two minutes and longer. In some cases the tetanic effect would appear only after very large doses of bile—6, 7, or more c.c. Some frogs would survive mild tetanic attacks and be in good condition again. Animals which had violent or prolonged tetanic attacks as a rule did not recover. Such frogs behaved as if they had been poisoned with a toxic dose of strychnine. None of the frogs which received the bile of this group have ever shown symptoms of coma and paralysis.

19. The bile of the first group, which produced predominantly coma, was already toxic in small doses. The bile of the third group, which produced, essentially, convulsions, exerted a toxic effect only in larger doses. The bile of the intermediary group, which produced hyperæsthesia in smaller and coma in larger doses, possessed only a medium toxicity: 2 c.c. of this bile rarely produced any effect.

We met with no bile which produced coma with smaller and convulsions or even hyperæsthesia with larger doses.

20. This series of experiments established, then, beyond doubt that the bile of some rabbits, at least, possesses a very pronounced tetanic element. In the bile of some animals the tetanic element was the only noticeable toxic agent. In the bile of the animals which possessed the depressing element as a toxic agent in a moderate degree, the tetanic element manifested its presence only by hyperæsthesia, and only in doses which did not

yet exert a depressing effect. Only in such bile of animals which exerted a very strong depressing effect upon frogs, causing coma and paralysis with comparatively small doses, no signs of the presence of a tetanic element could be discovered.

The question now was, Does the bile of animals which produced only coma and paralysis actually contain no tetanic element at all? From the behavior of the bile of the intermediary group we have reason to assume that the element which produces coma and paralysis when present in sufficient strength is capable of suppressing the manifestations of the tetanic element. It would therefore be conceivable that, even in the very depressing bile of the first group, a tetanic element is present, but that the depressing element is prevalent to such an extent that it is capable of completely suppressing any manifestations of the tetanic element.

21. Following out this assumption we came upon a plan which helped to demonstrate the presence of the tetanic element in the bile of all the rabbits we had tested.

In the intermediary group we have observed that a medium dose of bile was capable of bringing out hyperæsthesia, although the bile surely contained a certain amount of the depressing element. The reason for the success rested apparently in the fact that in this dose of bile, which was subminimum for the depressing effect, the mutual relations between the tetanic and the depressing elements were in favor of the tetanic agents. We now thought that by artificially supporting the tetanic element where present in the bile in subminimum doses we might also be capable of bringing out hyperæsthesia, and even convulsions. As an artificial means of support we thought of employing ineffective doses of strychnine.

In a foregoing paragraph we have mentioned that our previous experience led up to the question whether some dose of strychnine or of a tetanic element of catabolic origin might not be capable of overcoming or neutralizing to some extent the depressing effect of the elements producing coma and paralysis.

Stimulated by these questions we carried out several series of experiments in which the effects of bile, supported by additional injections of strychnine, were studied.

22. Series VI. *Bile and Strychnine Injected into Frogs.* In a few cases strychnine was added to the bile in a certain proportion

and kept for some time before the mixture was injected into the frogs. In most of the experiments, however, strychnine was injected consecutively and in another place than where the bile was injected. In the majority of the experiments such doses of strychnine were injected which were known from extensive previous experience to produce no effect at all, or a very slight one. In addition to this, in the majority of experiments the dose employed was specially tested in a control experiment. In the present line of investigation an extensive number of groups of experiments were made. We may state at the outset that in all cases the addition of a subminimum dose of strychnine brought out perceptible effects, which were not seen in the control experiments, whether with strychnine alone or with bile alone. We shall illustrate some of these results by citing a few experiments.

GROUP I. Bile from nephrectomized animals and strychnine were mixed in proportion of 1:10,000, kept for twenty-four hours, and then injected into frogs.

Frog A, control; injected into dorsal lymph sac 0.01 mgr. of strychnine nitrate at 3.17 P.M.; observed until 5 P.M.; no increase of reflexes; normal; next day normal.

Frog A′, same size as control (both small); injected into dorsal lymph sac 0.1 of the mixture (0.1 bile + 0.01 mgr. strychnine) at 3.22 P.M.; 4.07, reflexes distinctly increased; 4.15, violent tetanus. Next day frog normal again.

Frog B, control; injected into d.l.s. 0.02 mgr. strychnine nitrate at 11.23; at 12.15 P.M., no increase of reflexes; 12.55, reflexes slightly increased; 1.10, on handling, a mild tetanic attack; passed over soon,

Frog B′, same size as control (small); injected into d.l.s. 0.2 of the bile mixture (0.2 bile + 0.02 mgr. strychnine nitrate) at 11.28; 12.04 violent tetanus.

Frog C, large, control; injected into d.l.s. 0.05 mgr. strychnine nitrate at 11.52 A.M.; 12.53 P.M., no increase of reflexes; 1.15, reflexes increased; 2.10, reflexes markedly increased; 2.22, violent tetanus.

Frog C′, same size as control; injected into d.l.s. 0.5 of the bile mixture (0.5 bile + 0.05 mgr. strychnine nitrate) at 12 M.; 12.40 P.M., marked increase of reflexes; 12.53, violent tetanus.

23. The presence of a tetanic element in the bile of this group of experiments is quite evident. The doses of bile employed here never produced any hyperæsthesia, not to speak of a tetanus. We have, nevertheless, seen in all three experiments a well-marked increase of the efficiency of the strychnine by the addition of such small doses of bile. In experiment A the control, with 0.01 mgr. of strychnine, remained normal, whereas A′, with the same dose of strychnine, but with the addition of only 0.1 bile, had a tetanus. In B, with 0.02 strychnine, the control had a mild, brief tetanic attack on handling two hours after the injection, whereas with the addition of bile a violent tetanus set in spontaneously thirty-four minutes after injection. About the same occurred in experiment C—a violent tetanus after an hour in the bile frog and after two and a half hours in the control—both frogs being larger than in the two other experiments. In this series the addition of strychnine brought out the presence of a tetanic element in such doses of bile which otherwise are without any effect.

24. Group II. Frog A, control; injection of 0.01 mgr. strychnine nitrate; no effect. Frog A′, injected 0.01 mgr. strychnine + 1.5 salt solution (0.85 per cent.). After three and a half hours very slight temporary increase of reflexes (?). Frog A″, 0.01 strychnine + 3 c.c. salt solution. After three and a half hours slight temporary increase of reflexes (?). Frog A‴, 0.01 mgr. strychnine + 5 c.c. salt solution. The same as the others. All practically normal.

Frog B, injected 1.5 c.c. bile from common duct of a normal rabbit at 10.30 A.M. Condition unchanged; next day the same; normal. Frog B′, injected 1.5 c.c., same bile as above, and immediately after injected 0.01 mgr. strychnine nitrate at 10.30 A.M. At 2 P.M., reflexes markedly increased, and at 2.10, on handling, tonic rigidity. At 6.30, reflexes still increased; next day frog perfectly normal.

Frog C, injected 3 c.c. of the above bile at 10.30 A.M. At 2 P.M., increased reflexes; soon coma. At 6 P.M., dead.

Frog C′, injected 3 c.c. bile and immediately after 0.01 strychnine nitrate. At 2 P.M., increased reflexes; no coma. At 6.30 P.M., reflexes markedly increased and no coma. Next day animal perfectly normal.

Frog D, injected 5 c.c. of normal bile; at no time increased

reflexes nor coma and paralysis, and later in the day the animal was found dead.

Frog D′, injected 5 c.c. of the normal bile at 11 A.M.; animal soon droopy; injected 0.01 mgr. strychnine. One hour after the injection of strychnine a tetanus broke out; 6 P.M., animal still tetanic. Recovered next day and remained perfectly normal.

25. This group of experiments is very instructive. Doses of strychnine, the ineffectiveness of which was established in many controls, brought out distinct specific symptoms when given with bile; and with the increase of the dose of bile, although the dose of strychnine remained the same, the strychnine symptoms increased in intensity, so as to bring out a distinct tetanic state, lasting many hours. This can only mean that the normal bile contains a tetanic element, or an element which, in its effect, is similar to that of strychnine.

Moreover, this experiment demonstrates another still more important fact. In C and D doses of 3 and 5 c.c. of normal bile produced coma, paralysis, and death, whereas in C′ and D′, by the addition of a subminimum dose of strychnine, not only was a tetanus brought out, but coma and paralysis were overcome and the animals survived the deadly dose of bile.

26. In the experiments with the bile from the common duct of normal rabbits (without addition of strychnine) it was established, as stated above, that the bile of some animals, when given in comparatively large doses, produces hyperæsthesia and convulsions. This means that in such doses the tetanic element is present in the bile of these animals, at least in minimum toxic doses.

The bile of some other animals produces coma and paralysis in comparatively small doses. We have now demonstrated that even this bile contains a tetanic element. That it fails to manifest its presence when injected without the addition of strychnine is probably due to the overpowering influence of the depressing element in this bile. We have already seen in some of the cited experiments, and it will be seen later more fully, that the depressing element in bile, when present in effective strength, is capable of completely effacing the effects of a tetanic element, be it strychnine or a substance of metabolic origin.

Finally, the bile of some animals could be injected into frogs even in quantities of 3 or 4 c.c. without causing any toxic effect,

neither of one kind nor another. This might have been due to the fact that in this bile neither of the toxic factors was present in the above-mentioned doses in such strength as to produce a toxic effect. We have, however, reason to assume that in some instances, at least, the tetanic elements in the employed doses were strong enough to produce hyperæsthesia, and even convulsions. The harmlessness of the bile in these cases may have resulted, however, from the simultaneous presence of the depressing element in doses sufficient to neutralize the tetanic effect. We have seen above that in some cases a certain dose of the bile alone would produce coma, but when a subminimum dose of strychnine was added to this same dose of bile the effect could be a tetanus. This means that the tetanic element of the bile plus the subminimum dose of strychnine were capable of antagonizing the fatal dose of an effective strength of the depressing element to such a degree as even to produce a toxic effect in the opposite direction—namely, a tetanus. We can, under these circumstances, easily conceive that were the strength of the tetanic element in the bile slightly less the result would have been a simple neutralization—neither coma and paralysis nor tetanus—the frog simply appearing to be normal.

Such neutralizations might occur in many ways. There might be, for instance, a certain kind of bile which, in a certain dose, contains exactly a minimum dose of the depressing element. The result would be coma and paralysis were it not for the simultaneous presence of the antagonistic tetanic element in some weak strength, but sufficient to neutralize a fraction of the depressing element, thus reducing it to an ineffective strength; or the tetanic element might be present in an exactly minimum strength and the depressing element in a fraction of a minimum dose. Neutralizations might, of course, also occur when both antagonistic elements are present in minimum doses, or above them, provided they are present in such proportions as to be exactly sufficient to neutralize one another.

27. We have to state, however, that such cases as above quoted, where the paralyzing effect of doses of 3 and 5 c.c. of normal bile were completely overcome and turned into the opposite effect by the addition of strychnine were not of very frequent occurrence. We met them mainly in such bile in which the depressing

effect came out only when administered in larger doses. As a rule, when the dose of bile was sufficient to produce complete paralysis and coma already in moderate doses, the addition of strychnine was of no avail, or rather had a contrary effect, as we shall see later. In cases, for instance, where the bile produced complete coma and paralysis with a dose of 2 c.c., we never succeeded in overcoming completely the effect by the addition of strychnine, although even in these cases some degree of neutralization could sometimes be noticed, as is illustrated in the following experiment:

GROUP III. Bile from the dilated common duct of a rabbit. (The common duct was ligated for three days.)

Frog A, injected 0.6 c.c. bile; complete coma and paralysis in one hour.

Frog A′, injected 0.6 c.c. bile + 0.005 mgr. strychnine nitrate. Some coma; increased reflexes; condition decidedly better than in A.

Frog B, injected 1 c.c. bile; after one hour coma and paralysis, but alive.

Frog B′, injected 1 c.c. bile + 0.005 mgr. strychnine nitrate; coma and paralysis very soon; dead at the end of an hour.

Here in A′ the addition of a very small dose of strychnine was apparently instrumental in reducing the toxic effect of the very depressing bile. (The effect of B′ we shall discuss later.)

28. The last two series of experiments have acquainted us with two new important facts. 1. That rabbit's bile surely contains a tetanic element. 2. That the depressing and the tetanic elements within the bile are antagonistic to one another, and are capable of mutual neutralization, at least to a certain degree. Regarding the mutual relations of the antagonistic factors as they actually exist within the bile, we have so far learned the following facts: In the bile of the gall-bladder or of the ligated common duct the depressing element is apparently the chief factor. The bile produces only coma and paralysis, and is toxic in comparatively very small doses. The presence of the tetanic element can be detected only by the addition of an ineffective dose of strychnine, and even not in a very pronounced manner. A perfect neutralization is impossible.

The bile obtained from a fistula from the common duct is, in general, by far not so toxic as that from the gall-bladder. As to the particulars, there is an individual variation among the rabbits.

The bile of some rabbits is already toxic in comparatively moderate doses—2 c.c. and less. In this bile again the depressing element is predominant, the effect being coma and paralysis, and it is impossible to neutralize it by the addition of strychnine. However, in doses which are not yet toxic it is not difficult to bring out the effect of the tetanic element in this bile by the addition of an otherwise ineffective dose of strychnine.

In bile of other animals again the depressing element seems to be absent, at least it was so in doses which we have employed (not more than 10 c.c.). Here the bile alone will produce a tetanus readily, but only when given in comparatively large doses—5 c.c. and more. The addition of strychnine (ineffective dose) will bring out a tetanus with a somewhat smaller dose, but not with doses smaller than 2 c.c. In this bile apparently the tetanic element also is present only in small quantities.

Finally, the bile of some rabbits produces hyperæsthesia in doses of 2 or 3 c.c. and coma and paralysis in larger doses. Here the addition of strychnine to comparatively small doses of bile (1 to 3 c.c.) will produce a tetanus. The addition of strychnine will bring out a tetanus also with doses of this bile just sufficient to bring out (without strychnine) coma and paralysis. When the dose of bile is distinctly above this minimum, coma and paralysis will be the result, even if strychnine is added. Both elements are present and struggling against each other. In larger doses the depressing element is the victor; in smaller doses the tetanic element is capable of manifesting its presence, but produces only moderate symptoms. In doses near the border-line the addition of strychnine is capable of turning the balance in favor of the tetanic element.

29. The sum of observations seems to demonstrate:

1. That there is for the depressing element a definitely effective minimum, which, when present in a dose of any bile, overcomes nearly completely the antagonistic tetanic element, no matter in what strength it is present.

2. That bordering on this effective minimum there is another minimum strength of the depressing element, which, when present alone, or nearly so, can produce coma and paralysis; but this effect can be overcome by the antagonistic tetanic element when simultaneously present in the bile in a strength sufficiently above its minimum.

3. That this last minimum of the depressing element, or a strength weaker but near to it, when mixed with a minimum effective dose of the tetanic element might lead through mutual neutralizations to normal effects.

4. That the tetanic element when alone is efficient in a much smaller strength than the one which is required for the depressing element to be efficient; in other words, the efficient minimum for the depressing element lies higher than the minimum for the tetanic element.

With these relations of the antagonistic elements in mind we can easily understand why some bile causes only depression, other bile only hyperæsthesia and convulsions, and still other bile produces hyperæsthesia in smaller and coma and paralysis in larger doses.

30. With these relations in mind we may conceive, however, also such bile which would cause hyperæsthesia, or even tetanus, in smaller doses, normal conditions with next larger doses, and, finally, still larger doses would bring on coma and paralysis. Such apparently paradoxical conditions would occur when both antagonistic elements would be present in the bile simply in relatively minute strengths. The gradual increase of the dose of the bile would first bring the tetanic element up to its effective minimum, while the depressing element would still be far below its effective strength. (See 4.) The result would be hyperæsthesia, or even convulsions. A further increase in the dose of this bile would also bring the depressing element up to a strength approaching its effective minimum, which would be just sufficient to neutralize the tetanic element, even in its present strength. (See 3.) The result would be an apparently normal condition. Finally, a further increase of the dose of bile would bring the depressing element up to such an effective strength which is capable of completely overcoming the tetanic element in any strength (see 1); hence the coma and paralysis.

With such paradoxical effects of the bile we have actually been confronted in a few instances, especially in the experiments with additions of subminimum doses of strychnine. The following protocols are illustrations:

GROUP IV. Frog 1, injected 1.5 c.c. of bile from nephrectomized animals at 11.20 A.M. 2 P.M., frog normal; 6 P.M., rigidity of legs on handling; next day, normal.

Frog 2, injected 3 c.c. of same bile at 11.10 A.M. 2 P.M., normal; 2.30 P.M., somewhat "stupid," otherwise normal; no increase of reflexes; next day normal.

Frog 3, injected 5 c.c. of same bile at 11 A.M. 2 P.M., coma and paralysis; 6.30 P.M., dead.

31. In this experiment frog 2, with 3 c.c., had no rigidity or increased reflexes, and was in better shape than frog 1, with only 1.5 c.c. of bile; while frog 3, with 5 c.c., had coma and paralysis.

GROUP V. Frog 1, injected 1.5 c.c. bile from nephrectomized rabbit, and immediately after injected 0.01 mgr. strychnine at 11.20 A.M. 2 P.M., violent tetanus, passed into coma. 6.30 P.M., found dead.

Frog 2, injected 3 c.c. of same bile; then 0.01 mgr. strychnine at 11.30 A.M. 2 P.M., increased reflexes. 6.30 P.M., increased reflexes, somewhat comatose (?). Next day normal.

Frog 3, injected 5 c.c. of same bile; then 0.01 mgr. strychnine at 11 A.M. 2 P.M., coma and paralysis. 6 P.M., dead.

Here frog 2, with the larger dose of bile, had neither tetanus nor coma, and survived, while frog 1, with only 1.5 c.c., had both and died.

The rapid development of coma after a violent tetanus we shall discuss later.

GROUP VI. Frog A, injected normal bile 2 c.c. at 10.30. At 2, reflexes increased. 6 P.M., normal.

Frog A′, injected normal bile 2 c.c.; then 0.01 mgr. strychnine at 10.30. At 2 P.M., marked increase of reflexes, rigidity on handling. Next day normal.

Frog B, injected normal bile 3 c.c. at 10.30. At 2 P.M., stupor and paresis. At 6 P.M., coma and paralysis. Next day dead.

Frog B′, injected normal bile 3 c.c.; then 0.01 mgr. strychnine at 10.30. 2 P.M., normal. 6 P.M., normal. Remains normal next day.

Frog C, injected normal bile 5 c.c. at 11 A.M. 2 P.M., coma and paralysis. 6 P.M., dead.

Frog C′, injected normal bile 5 c.c.; then injected 0.01 mgr. strychnine at 11 A.M. 2 P.M., coma and paralysis. 6 P.M., dead.

In this experiment the addition of strychnine to 2 c.c. of bile brought rigidity, while the control remained normal. The addition of the same amount of strychnine to 3 c.c. of bile produced normal conditions, while the control died from coma and paralysis.

Finally, the addition of the same dose of strychnine to 5 c.c. of bile did not reduce the paralyzing effect of the large dose of bile. There was practically no difference between the strychnine frog and the control. The addition of strychnine then brought out first tetanic symptoms. When the dose of bile increased and with it the strength of the depressing element, the strength of the antagonistic elements were just sufficient to neutralize one another without leaving a balance for either side. When, finally, the depressing element increased considerably in amount it not only neutralized all tetanic effects, but had a sufficient balance left to produce paralysis and coma.

Such striking results, however, we have not met with very often. The success depends upon too many uncontrollable circumstances to be able to produce such results at will, or to meet them accidentally very frequently; but instances of less striking a character, in which the mutual neutralization of the two antagonistic elements was nevertheless very evident, were met with quite often, and some were, indeed, produced at will.

32. The addition of ineffective doses of strychnine to bile of nephrectomized rabbits brought out instructive observations. From the results in Series IV. we had reasons to surmise that a certain amount of a tetanic element of metabolic origin which normally passes through the urine in nephrectomized rabbits passed through the bile. In a number of experiments we took occasion to compare bile from nephrectomized rabbits with that of normal animals with regard to the effects of the addition of subminimum doses of strychnine. In the majority of experiments the difference was often, indeed, very strikingly in favor of the bile from nephrectomized rabbits—that is, the tetanic symptoms brought out by the addition of strychnine were more predominant in the experiments with bile from nephrectomized rabbits than in those with the bile from normal rabbits. We shall cite some such experiments.

Group VII. Frog A, injected at 3 P.M. 3 c.c. of normal bile, and then at 3.25 P.M. injected 0.01 mgr. strychnine. No signs of a tetanic effect. Paralysis; dead next day.

Frog A′, injected at 2.30 P.M. 3 c.c. bile from nephrectomized rabbit, and at 3.20 injected 0.01 mgr. strychnine. At 3.40, legs rigid; later, tetanus on handling; normal next day.

Frog B, injected 5 c.c. normal bile at 2.40 P.M., and at 3.25

added 0.01 mgr. strychnine. No signs of a tetanic influence. Coma, paralysis, and death.

Frog B′, injected 5 c.c. of bile from nephrectomized rabbit at 2.40, and at 3.25 added 0.01 mgr. strychnine. At 4.25, distinct rigidity on handling, and at 5.00, distinct tetanic attacks. Normal next day.

GROUP VIII. Frog A, injected at 12.30 P.M. 5 c.c. of normal bile, and immediately after 0.01 mgr. strychnine. 2.30, coma and paralysis; dead next day.

Frog A′, injected at 12.30 P.M. 5 c.c. of bile from nephrectomized rabbit, and immediately after 0.01 mgr. strychnine. 2.30, increased reflexes and rigidity of extremities. No coma. Next day reflexes still increased, and, on hitting table, mild tetanus. Survived.

In these and in some other experiments the addition of ineffective doses of strychnine to comparatively large doses of bile of nephrectomized rabbits produced tetanic symptoms, while the same doses of strychnine and normal bile produced coma and paralysis. In these cases nephrectomy apparently increased the tetanic capacity of the bile.

33. In the foregoing experiments we reported chiefly our manifold observations on the increase of the tetanizing element of bile by the addition of ineffective doses of strychnine. We have now to add that, under certain conditions, the addition of strychnine favors the appearance of the depressing effect of bile. Among the experiments described above instances were cited in which the addition of strychnine favored the appearance of coma and hastened the death of the frogs. Results of this character we have seen in a large number of experiments with rabbits, as well as with bile of other animals. Illustrative experiments we shall quote later, when we discuss our experiments with ox bile, where we met with such results quite frequently. Our results may be summed up as follows: When employing such doses of bile, which, when injected alone, were never capable of producing any degree of coma and paralysis, the addition of strychnine, whether in small or large doses, never favored the appearance of the depressing phenomena. If, however, the bile was of the type which caused the appearance of coma and paralysis quite readily, and the dose employed were such as would produce some degree of coma and paralysis sooner or later, the additional injec-

tion of strychnine would frequently hasten the onset of the depressing phenomenon, which would immediately attain an advanced stage. In some cases the sudden onset of coma would be preceded by a very brief, and sometimes even by a very violent, tetanus. The tetanus is usually so brief that it may have been frequently overlooked. The larger the added dose of strychnine the sooner would the tetanic effect appear, and the sooner would the complete coma and paralysis set in.

In cases where coma and paralysis are brought on by bile without the addition of strychnine, the development of the depressing symptoms takes place gradually and very slowly, especially when the dose of bile is not too large. The usual course is then as follows: After the animal gets over its first activity immediately on receiving the bile, and being put under the glass bell, it gradually becomes abnormally quiet, remains sitting in one place, and the head gradually sinks down to the table. When handled at this stage it becomes aroused for a while and jumps away like a normal frog, but as soon as it is left alone becomes droopy again. Soon it offers little resistance; very often it does not jump away, and when it does do so it jumps clumsily and only short distances. When turned on its back it makes only feeble attempts to turn on its stomach. However, it succeeds in doing so once in a while, and when again on its stomach draws its legs near the body; but head and stomach are now resting on the table. Gradually the limbs become limp, and in the attempts to move they get away from the body. They lose their tonicity and look œdematous. Soon the animal appears to be perfectly paralyzed. There are occasional sudden feeble twitches of some parts of the body; the respiration becomes feebler and slower; the heart beats also become slower. At this stage the pupils are generally constricted. In this condition the frog can remain for many hours before all signs of life become extinct. Between the injection and the state of complete coma and paralysis many hours may often elapse.

The course is entirely different when, in addition to an effective dose of bile, a dose of strychnine is added, especially when this dose approaches the effective minimum. On being put under the glass bell the animal becomes very lively; keeps its head high and is continually moving around. It is always near the transparent glass wall, looking for opportunities to escape from under the bell.

Suddenly, on hitting the table or handling the animal, and sometimes even without any visible cause, the frog is seized with a tetanic convulsion, and in a few seconds is lying stretched out on the table, nearly as paralyzed as a frog in the advanced stage of depression after receiving bile alone. Striking the table might still bring on brief responses of feeble stretching of the extremities, but in a short time there is no visible difference between the paralysis of the strychnine frog and the paralysis brought on by bile alone.

As to the cause of this paradoxical effect of strychnine, there are several possible suggestions. We may think, in the first place, of the fact that strychnine itself, as is well known, contains a certain depressing element, which becomes manifest after the tetanus is over, and we might assume that it is the addition of this depressing element to that of the bile which hastens the onset of the complete depression. Furthermore, it is probable that the sudden onset of the coma is always introduced, as we have already mentioned above, by a brief tetanus, which, on account of its brevity, is frequently overlooked. We may then assume that after the convulsive explosion the resistance of the tetanic element becomes momentarily exhausted; hence, the sudden appearance of the depressing phenomena. Finally, the apparently normal condition of the frog between the injection of the bile plus the strychnine and the outbreak of acute coma is upheld by a very unstable equilibrium between the two antagonistic elements. The sudden outbreak of the tetanic element disturbs this equilibrium, with the result that henceforth the stronger factor, here the depressing element, dominates the field. It is possible, also, that the acute outbreak is brought about by a combination of all the elements contained in the three separate suggestions.

34. We have stated that, after the outbreak of the coma and paralysis, the frogs remained in that state of depression until death. This is what happened in the great majority of experiments, and can be considered as the rule. In a few instances, however, the course was different. The first part of the course until the acute onset of the coma was the same as in all the other experiments. The further part of the course, however, would be strikingly different. The animal would lie there apparently in complete coma and paralysis. However, a stimulus of any kind,

such as touching the frog or hitting the table, would bring out a pronounced tetanic attack of short duration, which would pass rapidly into complete coma and paralysis. Sometimes such tetanic attacks would break out apparently spontaneously. This alternation between tetanus on the one hand and coma and paralysis on the other would continue for many hours, the condition reminding, in a striking way, of the syndrome in human pathology designated as eclampsia.

The quantity of strychnine employed in these cases had to be at least near the minimum effective dose; the quantity of bile, on the other hand, had to be not too much above the minimum dose, which, when employed alone, brought out coma and paralysis. When large doses of depressing bile were injected no such effect could be brought out by the addition of even a large dose of strychnine.

The tetanus occurring in these "eclamptic" cases was markedly in contrast with the tetanus brought out by bile alone. Each single tetanic attack in the latter cases lasted a long time, and, after passing off, a marked tonicity of the muscles remained, giving the animal a somewhat "graceful" appearance. Each tetanus in the "eclamptic" cases was very brief, and passed abruptly over into a perfect relaxation, giving the animals an œdematous look.

35. Finally, we have to add that when, after the injection of bile, coma and paralysis were already completely developed, the injection of strychnine, even of such doses as 0.04 or 0.05 mgr., hardly ever exerted any influence.

36. The paralysis which bile produces is, in the first place, of central origin. This has been demonstrated by Rywosch and others by direct experiments. We repeated such an experiment. In a case of complete paralysis produced by the injection of bile electrical stimulation of the cord produced no effect upon the muscles of the trunk or the extremities, while the stimulation of the sciatic nerves still produced quite active contractions of the extremities.

However, bile also affects directly nerve and muscle. This has been shown long ago by many observers. In our experiments we frequently had occasion to observe it in the following manner: In order that the large quantities of bile which we injected should not escape again, we used to reach the lymph sacs by passing the

needle through the muscles of the thigh, the muscles thus working as a valve. Now, these legs, especially the thigh, were often paralyzed long before there was any sign of paralysis in the rest of the frog. In some instances the frog would respond with a tetanus, in which even the lower part of the paralyzed extremity would take part. The paralysis of the thigh in those cases was caused, undoubtedly, by the bile coming in direct contact with the muscles of the thigh. This would mean that even such bile which failed to produce paralysis through the central nervous system would still reduce the irritability of the muscles by coming in direct contact with them.

37. The reduction of the irritability and conductivity of nerves and muscles by bile had probably some share in the advanced stages, and possibly, also, in the earlier stages of paralysis. Of the latter we had to think, especially when the injection of bile was given into the lymph sacs while the animal remained in its normal position, as was the rule. It might thus happen that some bile reached the sciatic plexus or nerves, causing hereby a premature local paralysis of the posterior extremities. Indeed, we met with such frogs which received ineffective doses of strychnine in addition to the bile, and in which the front legs became rigid, while the posterior extremities were paretic or paralytic. In a few cases, therefore, immediately after injecting the bile into the lymph sacs we have suspended the frogs by the legs, thus causing the bile to accumulate preferably in the anterior parts of the body. In these experiments it seemed, indeed, that the addition of strychnine brought out rigidity of the posterior extremities very readily and distinctly, while the animal seemed to be otherwise in a state of stupor.

38. We shall mention further that of the rabbits' bile which we have employed some was received sterile, some was sterilized, and some was exposed to boiling for half an hour before it was used. A few of the experiments with boiled bile made the impression that boiling reduces the effectiveness of the depressing element and favors the appearance of tetanus. However, the analysis of all the experiments does not justify such a positive claim. We may rather safely state that boiling does not affect pronouncedly either of the elements, but in a number of comparison experiments it was shown that boiling reduces the toxicity of the bile as a whole. The animals which received boiled bile

survived pronounced attacks of tetanus, as well as some conditions of coma and paralysis, whereas all the control animals with the same amount of unboiled bile and with otherwise the same symptoms died a day or two after the injections. Our experiments, however, were not extensive enough in this regard to permit a more definite statement.

The numerous facts communicated in the foregoing pages were derived, as frequently stated before, from an exclusive study of rabbits' bile. In the introductory remarks to this study we stated that we also studied the toxicity of bile of other animals, as well as the toxicity of bile salts. These studies were not as extensive as those devoted to the rabbits' bile, and were restricted to the ascertaining of only a few essential facts. We shall now very briefly report the results of these studies.

39. *Guinea-pigs' Bile.* We had at hand the bile of only three guinea-pigs. It was obtained from a cannula fastened either in the common bile duct or in the gall-bladder. We did not obtain much bile, and our observations were made only on a dozen frogs. The results were as follows:

2 c.c. or even 3 c.c. of the bile from the fistula caused no toxic effects of any kind. The frogs remained perfectly normal. 1 c.c. of stagnated bile from the gall-bladder had no effect either. The addition of 0.01 mgr. strychnine did not bring out any hyperæsthesia. The addition of 0.02 mgr. strychnine brought out, after many hours, distinct rigidity, while the control animal remained normal.

We bring these few results to record without attaching much importance to them. The observations were too few and insufficiently varied to permit positive conclusions. We may say, however, few as the experiments were, their number was larger than those from which some writers drew the positive conclusions as to the nature of the toxicity of bile.

From the fact that even 3 c.c. had no toxic effect we were at first inclined to the general conclusion that guinea-pigs' bile is less toxic than that of the rabbit, until we came across bile from such rabbits which was not toxic in doses of 3 c.c., but was definitely toxic in larger doses. It will have to be decided by a further more extensive study whether the bile of the guinea-pig is indeed less toxic than that of the rabbit.

40. *Dogs' Bile.* Our experience with dogs' bile is also very limited. However, the few experiments we made gave some

characteristic results which were in accord with the results obtained in the experiments with rabbits' bile. We shall illustrate them by two groups of experiments.

GROUP IX. Frog 1, control; injected 0.01 mgr. strychnine at 3.50 P.M. No effect.

Frog 2, injected 0.5 boiled dogs' bile (from fistula) at 3.50 P.M. No effect.

Frog 3, injected 0.5 boiled dogs' bile followed by an injection of 0.01 mgr. strychnine at 3.50 P.M. At 4.30, exaggerated reflexes, followed soon by a typical tetanus.

In this experiment 0.5 of the bile had no effect, but the addition of an ineffective dose of strychnine brought out a typical tetanus. That means that 0.5 of the dogs' bile contained a tetanic element large enough to convert a subminimum dose of strychnine into a toxic one.

GROUP X. Frog 1, weight 36 grams; injected 1 c.c. of dogs' bile at 10.15 A.M. At 12 M., complete coma and paralysis.

Frog 2, weight 42 grams; injected 1 c.c. of dogs' bile, followed immediately by an injection of 0.01 mgr. strychnine at 10.15 A.M. At 10.50, complete coma and paresis. 12 M., dead.

One c.c. of dogs' bile caused complete coma and paralysis in about two hours. The addition of strychnine hastened the onset of the depressing phenomena and the fatal termination—an experience similar to that which we frequently met in our experiments with rabbits, as fully described above.

We have not seen hyperæsthesia or convulsions occurring after injection of dogs' bile without the addition of strychnine. However, our experience with this bile was too limited to permit any conclusion from these negative facts.

41. *Ox Bile.* We employed ox bile as it was obtained from the slaughter-house, and also inspissated bile dissolved in various concentrations. Frequently the bile was filtered and sterilized before it was used. Our experience with this bile is quite extensive, and the few results we are going to report were safely established.

At the outset we have to point out that all ox bile is obtained from the gall-bladder, and we have to keep this in mind when comparing these results with those obtained with rabbits' bile.

Ox bile is very toxic. 0.3 c.c. will, as a rule, produce toxic symptoms sooner or later, with a fatal termination. The symp-

toms are nearly exclusively of a depressing character—coma and paralysis. In the numerous experiments we have made we came across tetanus only once. It was in a frog which received 0.3 c.c. bile (1.5 c.c. of a 20 per cent. — 1:4 NaCl 0.9), and which developed coma; but the next day the coma was interrupted by tetanic attacks—eclampsia. We tried much smaller doses, but never observed even hyperæsthesia as a consequence of injection of ox bile. This experience is similar to the one we had with rabbits' bile when obtained from the gall-bladder or from the dilated common duct. Stagnated bile is apparently very toxic and the depressing element in it is the controlling factor.

We had, however, numerous proofs of the presence of a tetanic element even in this very depressing bile. The following group of experiments is a good illustration:

GROUP XI. Frog A, injected 1 c.c. of a 10 per cent. solution of ox bile. Condition good; remains unchanged.

Frog A′, injected 1 c.c. of a 10 per cent. ox bile, followed by an injection of 0.005 mgr. strychnine at 4 P.M. At 6 P.M., increased reflexes.

Frog B, injected 1.25 c.c. of ox bile, 10 per cent. Condition good and remains so.

Frog B′, injected 1.25 c.c. of a 10 per cent. ox bile, followed by an injection of 0.005 mgr. strychnine at 4 P.M. At 5 P.M. violent tetanus.

In this series neither the employed doses of bile alone nor the dose of strychnine alone would produce any kind of an effect. When, however, both were given together the results were hyperæsthesia, or even tetanus.

Moreover, in some instances when the toxic dose of bile was on the border-line, and when given alone would sooner or later bring on depressing symptoms, with a fatal termination, the addition of some strychnine would still bring out a tetanus.

The following is an illustration:

GROUP XII. Frog 1, injected 0.25 of ox bile at 11.30 A.M. At 3 P.M. marked stupor. Next day dead.

Frog 2, injected 0.25 of ox bile, followed by an injection of 0.01 mgr. strychnine at 11.30 A.M. At 3 P.M. slight stupor. Next day distinct tetanus.[1]

[1] Such cases remind of the effect of certain doses of morphine upon frogs. On the day of injection there is either no effect or a moderate stupor, while a day or two later a distinctly tetanic condition develops.

On the other hand, we had many instances in which a dose of 0.01 strychnine, or more, when superadded to a distinctly toxic dose of ox bile would hasten the onset of the depressing phenomena, and also of a fatal termination. In some of these cases the coma, which was brought on acutely by the addition of strychnine, would not be of a continuous but rather of an "eclamptic" character, as was described above as one of the effects of rabbits, bile from a fistula.

There were some slight variations in the toxicity of the bile obtained at different times from the slaughter-house. Whether this variation was due to an individual variability of the animals we cannot state, since we are not sure that each portion of bile we received was obtained from only one animal.

The experiments with ox bile gave, then, instructive results. It is very toxic in already small doses, and is even more toxic than the bile from the gall-bladder of rabbits; and, like this bile, the toxicity is essentially of a depressing character. It produces coma and paralysis. However, by the addition of ineffective doses of strychnine it was satisfactorily demonstrated that even this very depressing ox bile contains a very effective tetanic element, the manifestation of which is suppressed by the overpowering antagonistic effect of the depressing factor. Furthermore, by the addition of strychnine to ox bile all the various phenomena were brought out which were observed in the studies of the addition of strychnine to bile obtained from a fistula of the common duct of rabbits.

42. *Bile Salts.* We have experimented with sodium glycocholate and sodium taurocholate separately. According to Rywosch,[1] for frogs weighing from 40 to 50 gm. the fatal dose of taurocholate is about 60 to 70 mgr. and of glycocholate about 100 mgr. Judging by his protocols, Rywosch had in mind such fatal doses which produced coma and complete paralysis in less than half an hour and death in less than two hours. Most of our frogs did not weigh more than 30 or 35 gm. Furthermore, we considered a dose of the bile as toxic when it produced any pronounced toxic symptoms within a few hours after injection of the bile salt. Our results, to sum up, were, briefly, as follows:

There were a few frogs which responded to an injection of 20

[1] Loc. cit.

mgr. of the bile salts, and there were a good many which responded to 30 mgr. with distinctly toxic symptoms and with a fatal result on the same day of the injection or within the next few days. In some instances even 40 mgr. had no positive effect, and exceptionally some effect was obtained even with 15 mgr. Injections with 50 mgr., or more, were invariably very toxic.

The toxic symptoms were of a depressing character—stupor and complete coma, paresis and complete paralysis. Beginning with small quantities and gradually increasing the doses of the bile salts until definite and fatal symptoms set in, we came across only one single instance for each salt of a tetanic effect of a doubtful character. These exceptions were as follows: With a dose of sodium glycocholate of 40 mgr. there were no perceptible symptoms on the same day, but on the next day some tonic rigidity seemed to be present. In another instance about half an hour after injection of 25 mgr. of sodium taurocholate coma developed, and while handling the frog a slight rigidity set in, which soon passed over into complete paralysis.

These two doubtful instances of temporary rigidity were the only signs of the presence of a tetanizing influence among the numerous experiments with the bile salts. There was in this regard no perceptible difference between the effects of the taurocholate and the glycocholate. We should also add expressly that, in disagreement with the above-mentioned statement of Rywosch, in our experiments there was no difference in the toxicity of the two salts.

The experiments with the addition of strychnine, also, did not bring out striking results in favor of the presence of a tetanic element in the bile salts. The addition of doses less than 0.01 mgr. never had the slightest effect. In the many experiments with additions of 0.01 mgr. strychnine to the injections of sodium glycocholate only once is noted slight hyperæsthesia. The same dose of strychnine (0.01) added to sodium taurocholate brought out in one case (10 mgr. + 0.01 mgr. mixed) a passing tetanus after two and a half hours, and in another case (30 mgr. + 0.01 mgr.) a slight tetanus. In the many other experiments with the taurocholate (0.01 and 0.015 of strychnine) there was no effect, except, perhaps, a slight hyperæsthesia in one or two cases. The addition of 0.02 mgr. strychnine to sodium glycocholate brought out tetanus in two experiments, while the control (with strychnine

alone) gave only hyperæsthesia. In other instances there were only increased reflexes. The same experience we had with taurocholate of sodium.

In a few instances the addition of a larger dose of strychnine hastened the onset of the coma. Two of the above-mentioned attacks of tetanus were the precursors of such an acute onset of the depressing phenomena. Coma and paralysis continued in these cases until death, except in two cases, where the course was of a typically "eclamptic" character.

The general conclusions which our experiments with the bile salts may permit us to draw seem to be that the toxic effects of bile salts upon the general nervous system are, indeed, essentially of a depressing character. The bile salts probably also contain some of the tetanic element, but in a very small degree. The addition of strychnine is here distinctly less effective than even in the experiments with bile which comes from the gall-bladder, and the toxic effects of which are also distinctly depressing in character.

43. Reviewing our results, we shall now trace our steps backward. The investigation which we carried on in the attempt to solve our original problem led up to a new question, which henceforth became the major-subject of the present research. It led us to the question as to the actual nature of the toxicity of bile. In answer to this question we obtained quite a large number of facts. Let us now see what they signify.

As we have stated in the introduction to this paper, it is now generally accepted that the toxic effects of bile are only of a depressing character. In our studies we found this to be true for bile from the gall-bladder, at least as far as the actual effect is concerned. Rabbits' bile from the gall-bladder produced only coma and paralysis. The same was the case with ox bile, which, as a rule, is obtained from the gall-bladder. Both were toxic in very small doses, the ox bile even more so than the bile from the rabbit. In the few instances we have tested, dogs' and guinea-pigs' bile from the bladder also produced coma and paralysis, and also with comparatively small doses. The same was true also of the bile salts. Sodium taurocholate and glycocholate, when injected into frogs in toxic doses, produced, as a rule, coma and paralysis.

It was different, however, with bile obtained from a fistula of the common duct of rabbits. The bile of some rabbits produced

only hyperæsthesia and true tetanic attacks, but never coma and paralysis. The bile of other rabbits produced marked hyperæsthesia with smaller doses and coma and paralysis with larger doses. Only in a few of the rabbits of our experiments did the bile from the duct produce only coma and paralysis, and no signs of increase of excitability. Here we had a positive direct proof that the normal bile from a good many rabbits had an exciting element, and its toxic effect upon frogs consisted in some cases only in the production of clonic and tonic convulsions.

Moreover, we found that small doses of any kind of bile would cause hyperæsthesia and tetanic attacks when they were supported by small doses of strychnine. The doses of the bile, as well as of the strychnine which come into play in these experiments, were so small that each agent separately produced no symptoms in the control experiments, whereas when given together they brought out typical convulsions. This could mean only that the bile contains an element which, like strychnine, can produce increase of excitability, and which, in the causation of such an effect, it can supplement and can be supplemented by it. We designate it for brevity's sake as tetanic element. By this method—*i. e.*, by the method of adding subminimum doses of strychnine—we have demonstrated the existence of a tetanic element also in such bile of the common duct of rabbits which gave only depressing symptoms. We also demonstrated its presence in the bile of dogs, in ox bile, and in rabbits' bile from the gall-bladder; in short, in all kinds of bile, and even in such a one which, when injected alone in toxic doses, gave only depressing phenomena. The evidence for the presence of a tetanic element in the bile salts was not very strong. If present, it is apparently there distinctly less quantitatively than in the whole bile.

We may therefore claim that our experiments have established the fact that bile contains a tetanic element which, when obtained from the common duct of some animals, at least, may manifest its presence without the aid of strychnine; and in some instances it may even appear to be the sole toxic agent present in that bile.

44. The bile of the gall-bladder of all animals produces only depressing symptoms, although it surely contains a tetanic element. The same can be said of bile stagnated in the ligated common duct, if the stagnation be not of too long duration.

From Series II. and III. it would appear that bile which was

obtained soon after the preparation of the fistula is apt to cause, preferably, depressing symptoms.

Furthermore, in some animals, as stated above, all the bile from the common duct produced only coma and paralysis, and with comparatively small doses.

We may add here that the flow of bile in these animals was slow, and the collected quantity small in comparison with the quantities collected from the animals, the bile of which produced hyperæsthesia and convulsions.

Considering all these facts together, we may, therefore, state that stagnated bile produces depressing symptoms.

Our experiments have demonstrated not only that all kinds of bile contain the tetanic element, but also that the tetanic and depressing elements are present simultaneously in one and the same bile. In stagnated bile, though it surely contains both elements, it is apparently essentially the depressing element which manifests its effects. What are the mutual relations of these two toxic agents?

Our experiments with the addition of strychnine has thrown some light on this very difficult question.

45. From a large number of varied experiments we have established:

1. That the depressing effect of large doses of bile cannot be reduced or visibly modified by the addition of any dose of strychnine.

2. That the depressing effect of doses of bile in the neighborhood of its toxic minimum can be promptly modified by some subminimum doses of strychnine. (*a*) The effect can be neutralized, annihilated. The result is a normal condition. (*b*) The depressing effect can be overcome to such a degree as to bring out an opposite effect—tetanus.

3. That by an increase of the depressing element within the bile the positively tetanic effect of the strychnine plus the tetanic element can be (*a*) neutralized, reduced to normal, and (*b*) converted into the opposite effect—coma and paralysis.

These observations lead us to assume, in the first place, *that the depressing and tetanic elements are exact antagonists, and that their joint effect is that of an algebraic sum;* that, furthermore, when each of the antagonists is simultaneously present in the bile in a distinctly effective minimum the effect of the depressing

element is by far the stronger, so as to conceal any modifying effects of its antagonist; that, however, the tetanic element attains its minimum effectiveness already in a much smaller dose than that which is required for the effective minimum of the depressing element.

On the basis of these relations we can explain the following combinations:

When the depressing element is present, either in a large or small dose of bile in a distinctly effective minimum, the result of an intoxication will always be depression—coma and paralysis.

When the tetanic element is present within any quantity of bile in a strength which is its minimum or above it, while the depressing element is far beneath its own minimum, the result will be hyperæsthesia, and even tetanus.

When both elements are present within the bile in minute quantities, very small doses of that bile will be harmless. With the increase of the dose first a stage will be reached in which the tetanic element will attain its minimum, reduced somewhat by the presence of the depressing element in a still very low strength. The result will be hyperæsthesia. In the next increase, when the effectiveness of the tetanic element will be more reduced by the increasing effectiveness of the depressing element, the result might be accidentally normal conditions, due to the exact mutual neutralization. The further increase of the dose will, of course, lead to the supreme reign of the depressing element. The middle stage, which depends so much upon precise neutralization, will be more often missed or overlooked.

The assumption, further, that the minimum for the tetanic element lies much lower than that for the depressing element,[1] in conjunction with the established fact that the definite minimum of the depressing element always overpowers the tetanic element, readily explains the fact that in stagnated bile the depressing element reigns supreme.[2]

In all of these considerations we have to remember, however,

[1] To mention an analogy the minimum toxic dose of strychnine (tetanic) is ten times lower than the minimum for morphine (depressing).

[2] Let us assume, for the sake of illustration, that D (epressing) = 2 T (etanic). Let us further assume that 4 c.c. contains D + 2 T; then 4 c.c. contains D + 2 T; then 4 c.c. will give coma and 2 c.c. (½ D + T) will give tetanus. When, now, the stagnated bile loses half of its water without losing its toxic elements, then 2 c.c. of this bile will contain D + 2 T, and the result will be that now 2 c.c. of this bile will cause coma and paralysis instead of tetanus.

that in the algebraic sums of both antagonistic elements none of the effect is actually lost—*i. e.*, if the result is some degree of coma and paralysis, we have to think that if it had not been for the simultaneous presence of the tetanic element the degree of depression might have been higher, and, *vice versa,* a certain tetanic effect would have been more pronounced if it had not been for the simultaneous presence of the depressing element in some strength.

46. The conditions and the relations which we have just been describing hold good only for stable relations—*i. e.*, when both antagonistic elements exist in firm relations to one another—in a stable equilibrium. When the mutual relations are loose, the equilibrium unstable, as would, for instance, happen when one or the other element was suddenly added in a certain strength to one of the antagonists, the outcome might be a struggle, either continuous or with early one-sided decision, instead of a uniform, well-balanced equilibrium. We have seen in our experiments that the addition of an effective dose of strychnine to an effective dose of bile can often bring out a very short tetanic effect, which immediately gives way to a premature onset of deep coma and paralysis. These depressions were either continuous till the premature death or there occurred a perpetual change between coma and convulsion—a state of eclampsia.

47. Finally, we have to point out that in the bile salts the tetanic element is apparently present less abundantly than in the whole bile. This fact does not agree well with the now generally accepted theory that the toxicity of the bile emanates exclusively from the bile salts. The assumption seems to be rather more acceptable that the tetanic element is intimately connected with some other part of the bile which, perhaps, has heretofore not yet been isolated, and that only a fraction of it clings to the bile salts. Here we should remember that in our experiments the tetanic element was not destroyed by prolonged boiling of the bile.

However, our series of investigations with the bile salts was not extensive enough to permit any final conclusions to be drawn in that regard.

48. The results of the last series of experiments which we have just analyzed demonstrated, indeed, that bile from the common duct of normal animals does contain a tetanic element

and produces occasionally convulsions; but they also demonstrated that the addition to this bile of a tetanic factor of any source will increase the tetanizing efficiency of that bile. We shall now examine in the light of the last experience the results which we obtained in the first few series of experiments.

In Series IV. we found that the bile from the common duct of nephrectomized rabbits was tetanic in character more frequently than the bile of the normal animals in Series V., and a good deal more so than the bile of the ante-strychnine period in Series II. (nephrectomized rabbits). We can now safely interpret this observation by the assumption which we had already previously suggested, namely, that normally a tetanic agent of catabolic origin is being eliminated in some degree through the urine.

After nephrectomy this tetanic agent finds its way, partially or totally, through the bile, and thus increases the efficiency of the tetanic agent normally present in the bile; hence, the increase of the tetanic effect of the bile of such animals.

In harmony with this interpretation is also the observation we made that the addition of strychnine to bile from nephrectomized rabbits increases the tetanizing effect of this bile more markedly than the addition of strychnine to bile of normal rabbits.

However, the bile of the ante-strychnine period in Series II. is, as we stated above, more or less stagnated; hence the prevalence of the depressing symptoms in the intoxication with this bile, the addition of the tetanic element notwithstanding.

In the post-strychnine period of Series II. the bile appeared to be more tetanic than the bile of any other series. We now assume that here some of the strychnine, at least, was indeed eliminated through the bile. The tetanic elements within this bile originated from three sources—the tetanic element of the bile itself, the strychnine, and some of the tetanic element ordinarily eliminated through the urine. Through the united effort of all the three agents the effects of the antagonistic depressing elements are considerably overcome; hence, the considerable increase of the exciting effects of the bile of this series.

The same applies to the bile of at least two normal animals of Series III. which received strychnine. An instructive incident is the observation in these cases that the urine of these animals had nearly no hyperæsthetic effect, while in normal animals the urine, as a rule, contains so much strychnine as to produce a tetanus.

Our explanation of the underlying conditions is as follows: Normally, strychnine is, indeed, eliminated through the bile into the intestines, but only to be reabsorbed, and to be gradually and finally eliminated through the urine. However, with the bile continually being discharged outside of the body through the fistula from the common duct, there is less chance for the strychnine to get into the urine.

Finally, in the first series of nephrectomized rabbits with ligated common ducts the strychnine had, indeed, diminished chances to leave the body; hence, the proportionately more frequent occurrence of tetanus in such animals than in animals which were only nephrectomized and then received subminimum doses of strychnine. Furthermore, it is possible that in some cases strychnine has been accumulated in the gall-bladder, but the biological test failed to demonstrate its presence on account of the overpowering effect of the depressing element in such stagnating bile.

Resume. From the preceding investigations we learned in the first place:

That, contrary to the prevailing opinion, bile contains a tetanic element, an agent which produces an increase of the excitability of the nervous system.

That bile from the common duct of many rabbits produces marked hyperæsthesia and tetanic attacks when injected into frogs.

That stagnating bile (in the gall-bladder, etc.) invariably produces coma and paralysis.

That the depressing and the exciting elements are mutual antagonists, the total effect of both, when simultaneously present in the bile, being that of an algebraic sum.

That the depressing element, when present in a pronouncedly effective dose, is by far the stronger of the two; while, on the other hand, the tetanic element becomes effective apparently in a dose far below that which constitutes the minimum for the depressing element.

That, owing to these peculiar characteristics of the two antagonistic toxic elements, the mixture of both within the bile can be so adjusted as to produce any of the many possible degrees of irritability lying within the range between tetanus at one end and paralysis at the other, including, also, such a neutralization, presenting an apparently tranquil normal state.

That bile salts seem to contain the tetanic element in a distinctly lesser degree than is usually present in the whole bile.

We learned, furthermore, that nephrectomy increased the toxicity of the bile in the direction of excitation.

That the same effect has been produced by subcutaneous injections of strychnine.

That the bile of nephrectomized rabbits which received strychnine produces hyperæsthesia and convulsions more readily than any other bile.

That, finally, by injecting a toxic dose of strychnine into a frog soon after it received a distinctly depressing dose of bile, in some cases an "eclamptic" state was produced—that is, a state in which convulsions alternated with coma and paralysis.

DISCUSSION.

Dr. Ewing: As I understand Dr. Meltzer, he tends to the theory that the liver is considerably concerned in the uremic phenomena. If so, his theory finds some support in the observations of pathologists, since Virchow is quoted as stating that in cases of uremia lesions of the liver are quite as frequent as those of the kidney. For some years I have been collecting material from cases of uremia. I have secured enough evidence to warrant me in stating that in a certain group of uremic cases there are very striking lesions in the liver. I have not found such lesions in all cases. In some cases very much more serious anatomic lesions are seen in the liver than in the kidney.

Dr. Cohen: Does Dr. Meltzer include or exclude in his studies what we are in the habit of calling chronic uremia? He speaks of the absence of symptoms until at a certain critical point we have an explosion. Clinically, it would seem that there are very many poisons concerned in the production of the symptoms that we have been in the habit of grouping under the head of uremia, and that some of these symptoms are almost constantly present in every case of nephritis. Sometimes there are rather slight spasmodic symptoms, muscular twitchings and the like, which the text-books know about, but I refer to a chronic intoxication of which the symptoms are vague and likely to be overlooked if one is not on the alert. The explanation of balanced poisons, a sort of mutual counteraction or equilibrium, among these different elements fits in very well with the clinical manifestations of chronic uremia, and it may well be that the explosion, giving one or another group of symptoms, might

be due to some critical disturbance of equilibrium, perhaps a failure to produce or failure to eliminate one out of the group of poisons which up to that point have been neutralizing or antagonizing one another.

Dr. Carroll: In a discussion on yellow fever some years ago I took the ground that in yellow fever the pathologic lesion is in the liver. There is also a marked fatty degeneration of the liver. We know, of course, that the liver is an organ that elaborates urea from the products of tissue metabolism, but where the liver is seriously damaged these changes of metabolic products into urea cannot take place properly if they are retained in the circulation in the form of carbonate of ammonia and lactate of ammonia, and it is these products that bring about these so-called uremic convulsions. I took that position and I am delighted to hear so much confirmation from Dr. Meltzer. In cases of puerperal eclampsia, though, the liver would be found to be diseased, and on autopsy the liver has been found the seat of excessive fatty degeneration or cirrhotic changes.

Dr. Meltzer: I certainly included so-called chronic uremia.

XANTHELASMA AND CHRONIC JAUNDICE.

By THOMAS B. FUTCHER, M.B. (Tor.),
ASSOCIATE PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

(From Prof. Osler's Clinic, Johns Hopkins Hospital.)

Xanthelasma, xanthoma multiplex or vitiligoidea as an accompaniment of chronic jaundice is a comparatively rare affection. This paper is based on three such cases admitted to Dr. Osler's wards at the Johns Hopkins Hospital. These constitute all the cases that have occurred in the hospital during the first sixteen years ending with May 15, 1905. During this period there had been 18,400 medical admissions, among which there was a large number with chronic icterus. All three cases were admitted between January 30 and June 26, 1901, two having been under observation in the same ward at the same time. The main points in the clinical histories of the cases follow:

Case I. (*Gen. Hosp. No.* 33,689).—*History of typhoid fever; later, cholecystitis; onset of symptoms of gallstones of the common duct two years after the typhoid infection; eight months after the onset of the jaundice, the xanthoma plaques made their appearance; xanthomata on gums; exploratory laparotomy; gallstones in the gall-bladder and common duct; spontaneous disappearance of the xanthelasma after leaving the hospital.*

L. J. F., female, white, married, aged thirty-nine years, was admitted to the Johns Hopkins Hospital on January 30, 1901, complaining of "jaundice."

The family history was unimportant, with the exception that her father had had three attacks of jaundice associated with enlarged liver, attributed to the use of alcohol.

The patient was healthy as a young woman. Married twenty-one years. One child eighteen years ago. Typhoid fever in June, 1897, about three and one-half years before admission. Attack lasted five weeks. After tempera-

ture returned to normal, but before she was out of bed she had a very severe attack of pain in the epigastrium, associated with vomiting. There was great sensitiveness in the upper abdomen, with fever of several days' duration.

The present illness dated from the summer of 1899, two years after the typhoid infection. It began with an attack of abdominal pain without jaundice. In December, 1899, thirteen months ago, she had several attacks of colicky pain in the epigastrium, after which she became jaundiced. These were accompanied by chills, fever and sweating. The epigastrium was described as being swollen and very sensitive. From that date there had been repeated attacks of the same character. Jaundice had been persistent, but varying somewhat in intensity. The stools were intermittently clay-colored. Patient lost fifty-three pounds in thirteen months.

The jaundice had existed for thirteen months. There had been severe pruritus. Five or six months ago, and eight months after the onset of the jaundice, she first noticed flat, yellow patches appearing on the palms of the hands, particularly in the folds of skin at the flexures of the joints. Later, others appeared in the folds of the elbows, over the olecranon processes, axillæ, sides of the neck and dorsal surfaces of the toes. At first flat, they subsequently became somewhat raised. The patches over the olecranon processes were sensitive on being struck, and those on the hands were also tender when she used the broom. Friction seemed to favor their occurrence. One particularly thick xanthoma patch developed beneath a ring on the third finger of the left hand. The finger became so sensitive that the ring had to be removed.

Physical Examination. The following were the essential features in the physical examination on admission: Patient still fairly well nourished. Uniformly jaundiced; sclerotics deep yellow in color.

Distribution of Xanthoma Plaques. One very small one on left upper eyelid. Large, flat, yellow patch on right side of neck, 3 x 4 cm. in diameter, with small outlying portions. Similar but still larger one on right side of neck. Smaller one over the fold of left trapezius muscle. *Right arm and hand.* Patch in fold of axilla. Areas of keratosis about elbow and numerous nodular xanthomata around them. Exactly corresponding to the fold of the elbow there was a long linear xanthoma with small outlying ones. Small patch over one of the creases at the wrist. Two in the palm of the hand over palmar creases. In the creases on the flexor surfaces of all the metacarpophalangeal and nearly all the interphalangeal joints there were xanthoma plaques, usually linear but occasionally irregular in outline. A few patches were scattered over the sides of the fingers and on the knuckles. *Left arm and hand.* The distribution of the lesions was so nearly identical with those on the right upper extremity that a separate detailed description is unnecessary. A few patches on the upper chest. None on abdomen. Few

on dorsal surface of the toes. All the patches had a distinct whitish-yellow tint, differing materially from the color of the jaundiced skin. The majority of the xanthomata were flat and not elevated. A few of the older ones were elevated and slightly nodular, particularly those on the extensor surfaces of the elbows.

The examination of the thoracic organs revealed nothing of importance. The liver was considerably enlarged. The absolute hepatic flatness extended 6.5 cm. below the costal margin in the mammillary line and 13.5 cm. below the tip of the ensiform in the median line. The gall-bladder was not palpable. The splenic border was rounded and palpable 5.5 cm. from the costal margin.

The stools were light in color but contained some bile. Urine contained bile-pigments. Blood coagulation time on admission was 8 minutes and 15 seconds.

On January 31st Dr. Osler made the following notes: "Interesting points in connection with the case are (1) sequence of typhoid, cholecystitis and gallstones; (2) chronic jaundice associated with delayed coagulation time; (3) chronic jaundice associated with the symptom-complex of gallstone in the common duct; (4) xanthelasma."

On February 1st I noted that there was apparently the same sort of lesions on the gums as were found on the extremities. The patches had an opaque yellow appearance and were slightly thickened. The lesion was most evident on the gum over the upper incisors and on that over the lower incisors and canines.

On February 27th a few fresh xanthoma patches were noted for the first time over the patient's back. Under the administration of calcium chloride the coagulation time of the blood became reduced to 3 minutes and 55 seconds.

Operation. On February 28th Dr. Halsted performed an exploratory laparotomy and found two large stones in the gall-bladder and one in the common bile-duct. There were no indications of xanthomata in the mucous membrane of the gall-bladder or bile-duct.

The patient did well until the eighth day, when she had a severe secondary hemorrhage from the wound. Later, she developed a fibrinous pleurisy and a pericarditis, from which she eventually recovered, and was discharged from the hospital much improved but still somewhat jaundiced on June 1, 1901.

Dr. Florence Sabin, who was Medical Interne in charge of the patient when she was in the hospital, followed the subsequent progress of the case and she has kindly turned over the notes to me. These may be briefly summarized as follows:

April 7, 1903. General health excellent. Still jaundiced. Operation wound healed after eighteen months. Has occasional attacks of soreness over the liver region which lasts a few days, during which time the urine becomes very dark.

March 9, 1905. Patient wrote that she was in excellent health and weighed 150 pounds. In reply to a question as to the present condition of the yellow patches she stated that they had entirely disappeared.

In this case the xanthomata were mainly of the flat variety, although there were a few of the nodular variety about the right olecranon. The jaundice had been present for eight months before the onset of the xanthomata. An interesting feature of the case was the spontaneous disappearance of the xanthomata after the patient left the hospital.

CASE II. (*Gen. Hosp. No.* 33,912).—*Gallstones of the common and hepatic ducts and of the gall-bladder; biliary hypertrophic cirrhosis; jaundice of ten years' standing; appearance of xanthomata eight years after the onset of the jaundice. Severe hemorrhages from the nose and uterus; death and autopsy.*

M. A. C., female, white, married, aged thirty-nine years, was admitted to the Johns Hopkins Hospital on February 19, 1901, complaining of hemorrhages.

The family history was unimportant. The patient had always been a healthy woman previous to the onset of the present illness. She was the mother of six children.

The present illness began ten years ago with what she described as "malaria." She had attacks characterized by chills, fever, sweating and paroxysmal pain in the right hypochondrium at the beginning of the attacks. Jaundice developed at the onset and has since continued with varying degrees of intensity. The attacks of pain, chills and fever have recurred at intervals up to the present. In March, 1900, she had severe hemorrhages from the nose and uterus, which lasted three weeks. Four days before entrance these recurred and became so severe that she sought admission to the hospital for them. For years "blood blisters," the size of a split pea, had appeared over the body, and she was liable to have bruises develop on the slightest injury.

Two years ago, and eight years after the onset of the jaundice, she noticed yellow patches developing on the palms of the hands and subsequently on other parts of the body. There were no symptoms referable to them.

Physical Examination. The following were the essential features in the examination: The patient was fairly nourished. There was intense jaundice, and extreme pallor of the skin and mucous membranes. The patient was very freckled. The lungs were clear on percussion and auscultation. The heart showed nothing of importance excepting a faint systolic murmur, probably anemic in origin, at the mitral area. The relative liver dulness began at the fifth rib in the mammillary line; the absolute at the sixth rib in the same line not extending quite to the costal margin. Just below the costal margin and inside the mammillary line there was an indefinite rounded mass

to be felt which descended on inspiration and suggested possibly a distended gall-bladder.

Xanthomata. On both of the upper and lower eyelids were long, somewhat-raised yellow plaques. In the lines of the palmar surface of both hands and along the sides of the fingers were similar plaques only less raised. The elbows, both flexor and extensor surfaces, and the axillæ had small rounded tumor-like nodules. Over both buttocks were numerous larger, round, raised, nodular, yellow masses varying up to 0.5 cm. in diameter. There were a few over the knees and dorsal surfaces of the feet.

There was a spontaneous subcutaneous hemorrhage over the right knee, and a continuous flow of pale bloody fluid from the vagina.

The urine contained abundance of bile pigments, a trace of albumin, but no casts.

On admission the red cells were 1,880,000 per c.mm.; the leukocytes, 15,700 per c.mm. and the hemoglobin 23 per cent. The coagulation time was 14 minutes. Under complete rest and the administration of iron the patient's condition markedly improved. On March 25th the blood count was as follows: red cells, 4,804,000 per c.mm.; leukocytes, 9,700 per c.mm.; hemoglobin, 58 per cent. Under calcium chloride the coagulation time on this date had become reduced to 4 minutes and 53 seconds. Her condition continued to improve and she progressively gained in weight. She refused an exploratory operation, and at her own request was discharged on April 18, 1901.

A few days after her discharge from the hospital the patient died, death having been preceded by severe uterine hemorrhages. Permission was obtained for an autopsy, which was made by Dr. W. G. MacCallum.

Anatomic Diagnosis. Cholelithiasis; obstructive jaundice; biliary hypertrophic cirrhosis of the liver; splenic tumor; acute nephritis; ovarian cystomata; xanthelasma multiplex.

The following were the chief features about the liver and bile passages: The common duct was plugged with a large plum-shaped gallstone. There were several gallstones in the gall-bladder almost embedded in saccules in the bladder wall. The hepatic duct was filled by a curved cylindrical concretion. Above this the gall-ducts throughout the liver were enormously thickened. The walls of the ducts were almost 0.5 cm. in thickness and of a deep-yellow color. On section of the liver the bile-ducts stood out everywhere looking like sclerotic arteries. There were some minute yellow flecks in the mucosa of the walls of the bile-ducts, but there were no lesions typical of xanthomata. The liver was large and measured 35 x 18 x 11 cm., and weighed 2800 grams.

The chief features of interest in this case were: (1) The combination of cholelithiasis with biliary hypertrophic cirrhosis as a

cause of the jaundice. (2) The development of the xanthomata only after the jaundice had existed for eight years. (3) The xanthomata were of two types, flat and nodular.

CASE III. (*Gen. Hosp. No.* 35,296).—*Hypertrophic cirrhosis of the liver; severe uterine hemorrhages; jaundice lasting one and a half years before the onset of the xanthomata; hemorrhages from the gums and uterus.*

L. H., female, white, married, aged forty-two years, was transferred from the surgical to the medical department of the Johns Hopkins Hospital on June 26, 1901, complaining of "liver trouble and jaundice."

With the exception of her father and mother having both died of tuberculosis the family history was unimportant. The patient had had six children and one miscarriage. She had been in the habit of taking an occasional glass of beer or porter for years; no whiskey. For several years she had suffered from attacks of abdominal pain, particularly after indiscretions in eating.

She dated her present illness from five years ago, when she began to have vertigo and general weakness and was forced to give up her work. Her bowels, which had been previously constipated, became rather loose. Two and one-half years ago jaundice developed, which had continued ever since. The stools were gray and the urine high colored. There had been no chills, fever or attacks of abdominal colic, although she had had indefinite pains in the left hypochondrium. For a year she had noticed a tender spot over the liver, the sensitiveness increasing with pressure or deep inspiration. For the same period she had suffered from repeated attacks of severe uterine hemorrhages. On November 19, 1900, she was admitted to the surgical side of the hospital. She was then jaundiced. The red blood cells were 1,504,000 per c.mm., and the hemoglobin 28 per cent. The coagulation time was between 3 and 4 minutes. Owing to the severe anemia an exploratory laparotomy seemed inadvisable. Her general blood condition gradually improved, and on May 31, 1901, Dr. Mitchell performed an exploratory laparotomy. Careful examination of the bile passages failed to reveal any gallstones. The liver was much enlarged and presented the appearances of an hypertrophic cirrhosis, which was the surgical diagnosis. The postoperative history was uneventful, and the wound healed well. The jaundice persisted, however, and on June 26, 1901, she was transferred to the medical side of the hospital.

For about one year previous to her admission to the medical ward she had noticed whitish-yellow spots appearing, one below the left eye, the other below the right. These had been gradually increasing in size.

Physical Examination. The patient was of small stature, but was fairly well nourished. Jaundice was intense. The lungs were normal. Over the apex of the heart was heard a loud blowing systolic murmur, which was transmitted to the axilla and was also audible over the body of the heart.

The liver dulness was considerably increased and extended about 6 cm. below the costal margin in the right mammillary line. The border could not be distinctly felt, owing to the tenderness over the hepatic region. There was considerable tympanic distension of the abdomen, but no ascites. The spleen was not palpable.

Situation of the Xanthomata. Over the lower right eyelid there was a flat yellow xanthoma patch measuring 1 cm. x 2 mm. Above and within the left internal canthus there was a similar one measuring 1.5 cm. in diameter. Careful search failed to reveal any xanthomata on any part of the body.

The urine contained abundance of bile pigments, but no albumin or casts were present.

During her stay on the medical side she had some bleeding from the lips and mucous membrane of the mouth. On July 4, 1901, she was discharged from the hospital at her own request.

The patient returned to the hospital for observation on November 28, 1904. The jaundice was still present. She had had some bleeding from the gums and from a scratch on the ear. The liver border was palpable three fingers' breadth from the costal margin.

In this case the xanthomata were confined to the eyelids. The patient gave a definite account of their appearing one and a half years after the onset of the jaundice. The case was therefore not one in which a patient with xanthomata of the lids developed a chronic jaundice, but the reverse. Although the xanthomata were not so widely distributed as in the previous cases, yet there was no reason to doubt that they were dependent on the hepatic disease or the jaundice.

Xanthelasma is not a common disease under any circumstances. The cases in which it is limited to the eyelids (*xanthoma palpebrarum*) occur much more frequently than those where the lesions are more generally distributed (*xanthoma multiplex*). The majority of the latter form are of congenital origin in the young, or associated with jaundice or glycosuria in adults.

Xanthomata occur in two forms: either as flat plates or plaques (*xanthoma planum*), or as nodules or tumors (*xanthoma tuberculatum* or *tuberosum*). According to Crocker they represent little more than differences in position, shape and degree of development.

Xanthoma palpebrarum constitutes the bulk of the cases, and the lesion here is in the form of *plaques*. It commences most

frequently on the left upper eyelid near the inner canthus and may form a semicircle of the whole eye. Later, the right side becomes affected and the lesion is usually symmetric. The patches have a chamois-leather yellow color. They are either not at all or only slightly raised and are situated in the corium. They are soft and smooth and the skin does not seem thickened when it is picked up.

Xanthomata when of the *nodular* variety have the same color as the plaques, but project more or less above the surface. They vary in size from a millet-seed to a large pea and in rare instances may be 2 or 3 centimeters in diameter. The small ones are convex, round or oval, and often have a fine network of capillaries over them. They are soft and smooth to the touch. The larger ones are made of conglomerations of the smaller ones, and are irregular in contour and are more or less firm in consistence, depending upon the amount of connective tissue they contain.

Xanthoma multiplex in the adult is most frequently associated with jaundice of long standing, and it is this form with which we are especially interested in this paper. The first reference I have been able to find of the association of xanthelasma with chronic jaundice is in a paper by Thomas Addison and William Gull,[1] published in 1851, and entitled "On a Certain Affection of the Skin, Vitiligoidea—*α*, Plana, *β*, Tuberosa. With Remarks and Plates." They report five cases of a skin affection with which they were not familiar, and, owing to a certain resemblance between it and the disease described by Willan as vitiligo, they suggested the name *vitiligoidea*. They distinguished two varieties of the affection: the flat, to which they gave the name *vitiligoidea plana*, and the nodular which they designated by the name *vitiligoidea tuberosa*. Of the five cases, three were in patients with chronic jaundice. In one of the three the lesions were distributed in the creases of the wrists, hands and interphalangeal joints similar to the distribution in Cases I. and II.

The lesions of xanthoma multiplex in chronic jaundice are both in plaques and nodules, the former type prevailing. They may

[1] Guy's Hospital Reports, new series, 1851, vol vii. p. 265.

involve the skin, mucous and serous membranes and the tendons. The commonest positions are the eyelids, where it is said to most often begin, the palms and soles and backs of the hands and feet, flexures of the wrists, and the buttocks in and near the cleft and about the anus. It is of interest to note that in Cases I. and II. the xanthomata made their appearance first on the palms of the hands. The plaques are most commonly found on the eyelids, joint flexures, and mucous membranes. In Case I. the gums were affected. In Case II. there were suggestive indications of xanthomata in the mucous membrane of the bile-ducts on macroscopic examination, a suspicion which was confirmed on microscopic study of the sections. The nodules usually occur on the extensor aspects of the joints, particularly on parts exposed to irritation, as the knuckles, elbows and knees. In xanthoma multiplex symmetric arrangement of the lesions is the rule and is often very striking. This was a marked feature of Cases I. and II., and was also true in Case III., in which the lesions were limited to the eyelids. The xanthomata appear gradually and are slow in their development. After months or years their growth ceases and there is usually no future change in them. Crocker states that three instances have been reported in which spontaneous disappearance occurred after several years. In Case I. the xanthomata had entirely disappeared within four years after the patient left the hospital, and about four and a half years after their first appearance.

The xanthomata rarely cause any inconvenience excepting from their disfigurement. Occasionally, burning, prickling or itching have been experienced, and when they have occurred on the palms of the hands or knees, grasping objects or kneeling may cause some discomfort or even pain.

In 1882 a committee composed of Jonathan Hutchinson, Alfred Sangster and H. Radcliffe Crocker[1] was appointed by the London Pathological Society to report on two cases of xanthoma multiplex, one of which was demonstrated before the Society by Stephen Mackenzie, and the other by James Startin. They

[1] Transactions of the Pathological Society of London, 1882, vol. xxxiii. p. 376.

collected data of 23 cases of xanthoma multiplex in adults with jaundice: 10 of these were in males, 12 in females, and in 1 the sex was not stated. It would seem, therefore, that women are a trifle more liable to the affection than men. They also found records of 5 cases of xanthoma multiplex in adults without jaundice: 4 of these were males and 1 a female. Statistics of 8 cases of xanthoma multiplex, either congenital or commencing before puberty, were also collected from the literature. It was not possible to definitely ascertain the sex in these cases, but 4 were believed to be males and 4 females.

Some of the conclusions of this committee regarding zanthoma multiplex were as follows: (1) That cases occurring before puberty, although structurally the same as those beginning at a later period, are etiologically different, have no traceable connection with hepatic disease, but are probably to some extent hereditary. That they may be congenital, and that the eyelids always escape. (2) That four-fifths of the cases of xanthoma commencing after puberty are associated with chronic jaundice from obstruction of the bile-ducts. That in some of the others the health has been perfect, but that diabetes has been observed more than once. That the eyelids are almost always involved and almost invariably the starting point. Occasionally spontaneous involution occurs. That as regards sexes the numbers affected are nearly equal.

From the standpoint of *etiology* there seems little doubt but that the jaundice is the exciting agent in the xanthoma multiplex cases accompanied by this symptom. The hepatic conditions causing the jaundice have been found to be cholelithiasis, stricture of the bile-ducts, atrophic and hypertrophic cirrhosis of the liver, hydatids and cancer. How the jaundice acts in effecting the changes in the corium is not known, but presumably it is through the agent of a toxin. Besnier, Hollopeau and Kaposi regard the jaundice and liver troubles as secondary and due to the development of the xanthomata in the viscera. Crocker states that the order of development of the clinical features does not support this view. It may be of interest here to note that Besnier and Gailleton have described a condition in hepatic

affections which they call *xanthochromia* of the skin, and not due to jaundice in some cases. It is more marked on the face and trunk than on the extremities, the conjunctiva and buccal mucous membrane are uncolored, and there is no bile in the urine and feces.

There is considerable difference of opinion as to the *pathology* of this skin affection. Xanthomata were excised from Cases I. and II., and the sections were carefully studied by Dr. W. W. Williams, of the Harvard Medical School, whose report has not yet appeared, but who has kindly furnished me with a copy of his histologic examination. In association with these cases sections from a xanthoma palpebrarum complicating a case of diabetes insipidus, admitted to the Johns Hopkins Hospital and reported by me before this Association last year, were also studied.

The findings in all three cases were practically identical, and I quote briefly the main features of Dr. Williams' report:

"The epidermis is essentially normal, although in places there are large vacuolated cells in the lower part. Below this is a layer of practically normal connective tissue, which, however, contains a few pigmented spindle-shaped cells. Branching off from this layer are numerous larger and smaller fibrous bands, becoming continuous with the normal tissue deeper down, and forming an irregular network. These trabeculæ are composed of fibrous connective tissue with a few deeply staining long narrow nuclei and some delicate elastic fibres. Also a few delicate pigment granules are to be seen.

"Within the meshes of this fibrous reticulum are masses of pale cells, although in places the same pale cells occur singly or in pairs between the connective-tissue fibres. Surrounding each cell in these groups is a delicate reticulum containing here and there fine elastic fibres.

"These pale cells (so-called xanthoma cells) vary much in size; and though some are small and mononuclear and others large and multinuclear, they are all otherwise similar. There is no definite cell membrane, and the protoplasm is everywhere finely granular and contains more or less refractive granules,

which react to the fat stains. Some of the cells are vacuolated and others definitely phagocytic.

"The nuclei are as a rule oval, with a distinct membrane, vesicular, and often contain several nucleoli. They are usually more or less centrally situated. Mitosis is seen in some of these pale granular cells. The number of nuclei vary from 1 to 20.

"About some of the bloodvessels, traversing these groups of cells, slight lymphoid cell infiltration has taken place. The endothelium of some of these vessels and of many lymph spaces is swollen and contains fatty granules. Also in the perivascular lymph spaces are seen pale, granular, vesicularly nucleated cells. In none of the specimens were any polymorphonuclear leukocytes, nerves or muscle cells found, or any involvement of the hair follicles or sebaceous or sweat glands noticed."

Dr. Williams' report on the histologic examination of the bile-ducts in Case II., which came to autopsy, is exceedingly interesting. "The walls of the bile-ducts are considerably hypertrophied, containing many elastic fibres, and the lumina are lined with a mass of lymphoid and plasma cells, and also many large, pale, granular, vesicularly nucleated cells, similar to those already described in the skin lesions." Apparently these changes were regarded as due to the development of xanthomata in the bile-ducts.

In a communication from Dr. Williams he wrote: "In my conclusions on these growths I maintained that they were of endothelial origin, though many described in the literature and also one I described are really lipomata—lipoma xanthomatodes."

The descriptions given by Crocker[1] and Touton for sections of xanthoma palpebrarum agree closely with Williams' report. There is no essential difference between the plaques and the nodular variety. In the latter the bulk of the lesion is more superficial and is in the papillary layer pushing up the epidermis above the level of the surrounding surfaces. The connective tissue is much more abundant than in the case of the plaques,

[1] Diseases of the Skin, third edition, p. 745.

and is most marked about the hair follicles and sebaceous glands. The fatty masses are less conspicuous and yellow oil globules infiltrate the meshes between the fibrous tissue. Crocker holds that in the development of the xanthomata inflammation is the primary factor, that the xanthoma cells and the connective-tissue growth are secondary, and that the whole process is of toxemic origin.

Köbner thinks that the lesions are derived from embryonic remnants. Török claims that the xanthoma plaque is composed of adipose cells interrupted in their progress to complete evolution, and that it is not a tumor but an excess of growth. Unna holds that the fat in xanthoma palpebrarum is a sort of fatty infiltration of the orbicularis muscle, the fat being in the lymph spaces and the giant cells being sections of dilated lymphatics. Politzer claims that the eyelid lesion is the product of the degeneration of embryonically displaced muscle fibres. This view has not been supported and seems to be disproven by the clinical fact that in both children and adults after the lesion begins on the eyelids it subsequently makes its appearance on various parts of the body.

There is no special difficulty in making a *diagnosis*. About the only condition likely to be confused with it is *milium palpebrarum*. These are usually small and situated near the inner canthus of the upper lid. Being due to retained sebaceous secretion, they are generally white and occasionally the dark-colored opening of the duct may be seen. Milium is more superficial and firmer, and the contents of the nodule can be easily peeled out. Politzer refers to cases of *multiple dermoid cysts* of the skin in which the diagnosis was possible only on microscopic examination of excised tissue.

After developing gradually for years the xanthomata become stationary and persist in the majority of cases throughout life. In rare instances, as in Case I., spontaneous involution may occur. In this case operation had been performed with a relief of the gallstone symptoms and almost complete disappearance of the jaundice.

There is practically no treatment for the condition, excepting

excision, that yields results. It seems almost certain that the xanthomata are due to the jaundice or to some associated toxic substance circulating in the blood. Consequently efforts should be made to relieve the causes of the jaundice, which is possible at least in the cases of cholelithiasis.

Summary. The three cases here reported were all in women, their respective ages being thirty-nine, thirty-nine and forty-two years. The duration of the jaundice before the xanthomata appeared was eight months, eight years and one and one-half years. The cause of the jaundice was gallstones of the common duct in two cases, one of which also had biliary hypertrophic cirrhosis of the liver, and in the third case hypertrophic cirrhosis of the liver alone. In all three cases the eyelids were involved, in one these only. In the other two there were lesions on the extremities and to a less degree on the trunk. In two cases the xanthomata appeared on the hands first; in the third on the eyelids. The xanthomata were chiefly in the form of plaques in all the cases. There were a few nodular xanthomata in Cases I. and II. The distribution was strikingly symmetric. In Case I. there were xanthomata on the gums, and in Case II. histologic examination of the bile-ducts showed that xanthomata of the mucous membranes of the ducts were present. At all events the histologic picture showed cells identical with the "xanthoma cells" of the lesions in the skin. In Case I. there was a spontaneous disappearance of the xanthomata four and one-half years after their onset and about four years after the gallstones were removed at operation. Two of the cases were operated on, and one came to autopsy so that the causes of the jaundice were definitely ascertained.

Four-fifths of the cases of xanthoma multiplex in adults occur in chronic jaundice. In these cases men and women are about equally affected, with possibly a slightly greater frequency in the latter. The hepatic conditions causing the jaundice have been found to be gallstones, stricture of the bile-ducts, atrophic and hypertrophic cirrhosis of the liver, hydatids and cancer. In addition to the skin, the tendons and mucous membranes may occasionally be involved. The onset is said to be most frequently on

the eyelids. The xanthomata accompanying jaundice are believed to be directly traceable to the latter or to some associated toxic substance circulating in the blood. Symmetry in distribution is often striking, and the tendency to develop in the folds and creases of the joints is a remarkable feature. The views as to the actual nature and sequence of tissue changes in the lesions vary much. Crocker thinks that inflammation is the primary factor and that the xanthoma cells and connective-tissue growth are secondary, and that the whole process is of toxemic origin. Williams' careful histologic study indicates strongly that the xanthomata are of endothelial origin. Once they develop they rarely disappear. Spontaneous involution is rare. No treatment other than surgical in suitable cases is of any avail. The indications are to relieve the underlying process if possible.

DISCUSSION.

Dr. Jacobi: I should like to ask Dr. Futcher if he includes those cases we see so very frequently of women who are getting old prematurely, and exhibit discoloration of the upper and lower eyelids? Do they belong to the same class? I have taken them simply for fatty degeneration or infiltration. Thirty or forty years ago I would cut them out, but advise patients now to let them alone, for they return. They are not malignant.

Dr. Futcher: The xanthomata referred to by Dr. Jacobi are somewhat similar to those under discussion, but are not identical. They are more of a fibrolipomatous character than are the true xanthomata in connection with jaundice.

A CASE OF LYMPHATIC LEUKEMIA IN A CHILD.

By JOHN LOVETT MORSE, A.M., M.D.,

AND

HARRY C. LOW, M.D.,

OF BOSTON.

Bessie C., a Jewess, was admitted to the Children's Hospital, on the service of Dr. Morse, August 23, 1904, when three and one-half years old.

Family History. The family history was negative. Her father and mother and four other children were well. There had been no miscarriages. There was no history of tuberculosis in the family or of exposure to tuberculosis.

Previous History. She was normal at birth; weighed nine and one-half pounds, and was nursed fifteen months. She had chicken-pox at six months, anterior poliomyelitis, involving the right arm and both legs, at eighteen months, whooping-cough at two years, and measles at two and one-half years. No sequelæ followed either the whooping-cough or the measles. She had practically recovered from the infantile paralysis, except that she used the right arm less freely than the left.

Present Illness. Loss of weight and strength, which began about the first of June, had progressed steadily, but slowly. There had been an increasing pallor during the same time. Her only complaints had been of a tired feeling and of pain in the ears. Her appetite had been poor, and she had had occasional attacks of abdominal pain followed by nausea and vomiting. The vomitus contained mucus and food, with some bile. There had been a slight cough for some weeks. Puffiness of the face and swelling of the neck had not been noticed until two weeks before entrance. There had been no hemorrhages.

Physical Examination. She was well developed and nourished and perfectly clear mentally. There was marked pallor of the skin, with a slight yellowish tint. The mucous membranes were pale. There was puffiness about the eyes. The ears and nose showed nothing abnormal. The tongue was moist and showed a thin, white coat. The throat was normal. There was no tenderness or rigidity of the spine. There was slight lagging of the right chest. There was dulness on the right side below the second rib con-

FIG. 1

Photograph at entrance.

FIG. 2

Photograph, Sept. 30th.

tinuous with the liver and heart dulness, and extending back to the anterior axillary line. There was hyperresonance over the rest of the right side. The respiration was diminished in intensity in the dull area and broncho-vesicular in character. The expiration was prolonged. Fluoroscopic examination showed a dark area corresponding to this area of dulness. The left lung was normal except for exaggerated respiration and an occasional sibilant rale. The cardiac impulse was visible and palpable in the fifth space in the nipple line. The upper border of the cardiac dulness was in the third space and the left in the nipple line; the right could not be determined. The action was regular; the sounds clear. The second pulmonic sound was decidedly the louder. The abdomen was full and tympanitic. There were no evidences of fluid or of new-growths. The lower border of the liver was palpable 4½ cm. below the costal border in the nipple line. The spleen was just palpable. There was considerable atrophy of the muscles of the right forearm, with a weakened grasp on that side. Both legs were a little weak and the muscles on the right were flabby. The knee jerks were present, but diminished, on both sides. The plantar reflexes were normal. There was no edema of the dependent portions. There were firm swellings, not tender; in the region of the parotid and submaxillary glands. There were many large, firm, non-tender lymph nodes, varying in size from that of a pea to that of a large cherry, in the postcervical, axillary and inguinal regions. The skin was not adherent over these enlarged nodes and showed no evidences of inflammation. The left epitrochlear gland was the size of a large pea, the right was not felt.

The urine was pale, acid, of a specific gravity of 1020, and contained a trace of albumin, but no bile or sugar. The sediment showed a large amount of ammonium urate and a few crystals of cystin.

The blood at entrance contained 45 per cent. of hemoglobin, 2,080,000 red corpuscles and 16,200 white corpuscles. A differential count was not made.

Fowler's solution was begun at once, but had to be omitted on August 30th because of vomiting.

The blood was examined again on August 31st, with the following result: Hemoglobin, 40 per cent.; red corpuscles, 1,765,000; white corpuscles, 19,000; small mononuclear, 58 per cent.; large mononuclear, 9 per cent.; polynuclear neutrophiles, 32.8 per cent.; eosinophiles, 0.2 per cent.

The red corpuscles showed considerable variation in size and moderate variation in shape. There was no polychromatophilia, but a little stippling. Two microblasts, 13 normoblasts, and 22 megaloblasts were seen in counting 400 white cells.

Although the percentage of the mononuclear cells, and especially of the small mononuclear cells, was large, it was felt that when the age of the child and the total number of white corpuscles were taken into consideration, the diagnosis of lymphatic leukemia was not justified and that search must be carried farther. It seemed possible to exclude syphilis in the family history and the absence of past or present signs of the disease. Tuberculosis was excluded because 3 mg. of tuberculin caused no reaction. No parasites or eggs of parasites could be found in the dejections.

Several small lymph nodes were removed from the left groin under ether, for pathologic examination, on September 1st. These nodes had the general outlines and, under low power, the appearance of lymph nodes. There was some general increase of the connective-tissue stroma. In many places the follicles were well distinguished; some of the lymph sinuses were filled with small lymphoid cells.

Studied under the high power (magnification 900 diameters) the cells were seen to be mostly small lymphoid cells, with the stroma pretty nearly uniformly distributed between them. Their nuclei were comparatively large and rather lightly stained, except for the numerous dark-blue chromatin granules. In many places they showed rather numerous mitotic figures. There were also great numbers of the larger type of lymphoid cells.

There were a number of large endothelial cells with large, irregular, vesicular nuclei and considerable cytoplasm. These seemed to be associated with the reticulum. There were a few polymorphonuclear neutrophiles. In places there was much blood in the lymph spaces, but no abnormal forms of red cells were seen.

Especially noticeable was the large number of eosinophiles that were present. There were occasional large cells, with one or more irregular vesicular nuclei. None of these were phagocytic, and, although not giant cells, they were similar to some of the large cells in sarcoma.

From this tissue a microscopic diagnosis of malignant lymphoma, or lymphosarcoma, was made, and (considering the

slightly altered condition of the blood at that time) the possibility of its being a case of beginning Hodgkin's disease was considered.

Three-quarters of a grain of citrate of iron was given subcutaneously every other day throughout September. The general condition improved decidedly during the first three weeks of the month. The appetite and digestion were much better. The color of the skin and mucous membranes improved quite markedly and the puffiness of the face diminished. The masses in the neck, the general enlargement of the lymph nodes, and the dull area in the right chest remained unchanged. The liver was palpable 5 cm. and the spleen 2 cm. below the costal border. The blood condition improved at the same time.

Examination of the blood on September 16th showed: Hemoglobin, 70 per cent.; red corpuscles, 4,800,000; white corpuscles, 29,000; small mononuclear, 56 per cent.; large mononuclear, 16 per cent.; polynuclear neutrophiles, 24.8 per cent.; eosinophiles, 0.2 per cent.; myelocytes, 2 per cent.; mast-cells, 1 per cent.

There was considerable variation in the size and shape of the red corpuscles, moderate polychromatophilia and slight stippling. Twenty-six normoblasts and 12 megaloblasts were seen while counting 400 white cells.

About this time interference with respiration during sleep developed. The breathing was noisy, although the mouth was kept closed. There was no enlargement of the tonsils and no increase of adenoid tissue in the throat. The obstruction appeared to be below the pharynx. Dr. Langmaid found no cause for the obstruction on examination, and thought that the trouble with the respiration was due to pressure of the growth in the chest on the nerve trunks. A nasal discharge, with a markedly septic odor, soon developed. Cultures from both nose and throat showed no Klebs-Loeffler bacilli. A firm new-growth then appeared in the posterior pharynx and increased somewhat in size. The obstruction to respiration and the nasal discharge, with the resulting septic absorption, caused a great deal of difficulty for several weeks; later they were much less troublesome.

About the same time that the difficulty with respiration

appeared the signs of a new-growth in the chest began to increase. Dulness developed under the sternum and to the left of the heart. The respiration on the right side was as before. The left chest moved less than the right and the respiration was decidedly diminished, although not changed in character. The masses at the sides of the face also began to increase in size; the lymph nodes throughout the body became larger and new ones appeared. The enlargement of the masses and lymph nodes increased progressively, and during the latter part of September the general condition fell off decidedly.

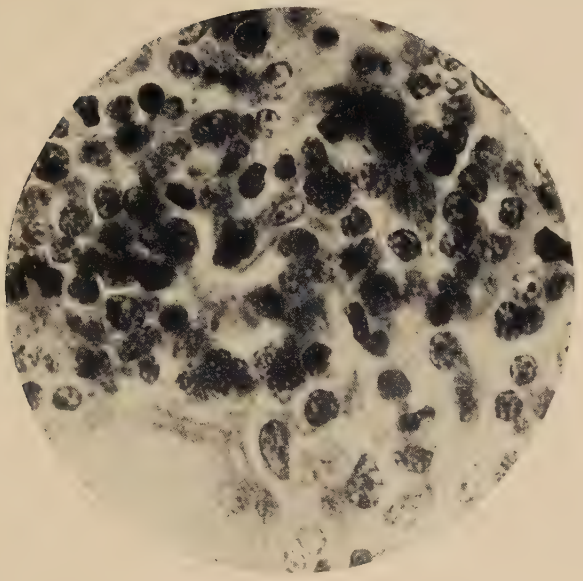
The examination of the blood, September 30th, resulted as follows: Hemoglobin, 70 per cent.; red corpuscles, 4,200,000; white corpuscles, 34,000; small mononuclear, 50 per cent.; large mononuclear, 12 per cent.; polynuclear neutrophiles, 34 per cent.; eosinophiles, 1 per cent.; myelocytes, 2.5 per cent.; mast-cells, 0.5 per cent.

There was moderate variation in the size and shape of the red corpuscles, with considerable polychromatophilia and slight stippling, Twenty-one normoblasts and 5 megaloblasts were seen while counting 400 white cells. Even at this time the diagnosis of lymphatic leukemia seemed hardly justified, that of Hodgkin's disease or lymphosarcoma seeming far more probable The patient then came into the charge of Dr. T. M. Rotch, owing to a change in service.

Lugol's solution, in doses of from 1 to 5 minims three times daily, was begun about the first of October and continued until death.

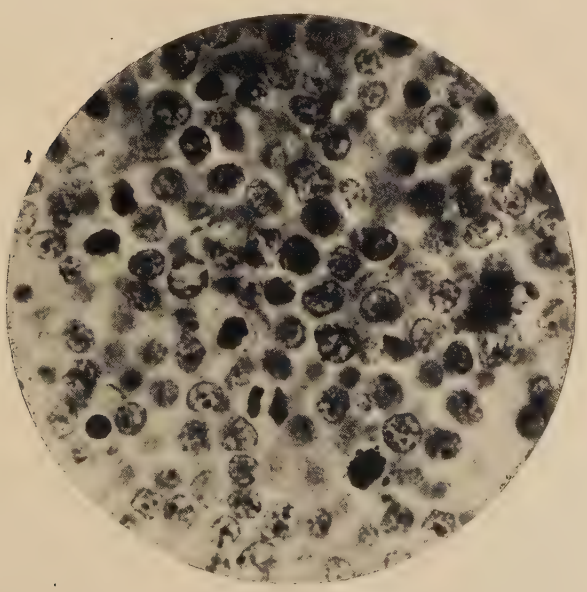
Early in October the gums became spongy and bleeding, and fine petechial spots appeared all over the body. A few large ecchymoses also appeared on the sacrum and thighs. About the middle of October there was a perforation of the hard palate on each side of the median line by a dark, soft, irregular substance resembling a new-growth about to break down. The blood picture changed materially as regards the differential count at this time. An examination of the blood, October 10th, by Dr. Richard C. Cabot, resulted as follows: Hemoglobin, 55 per cent.; red corpuscles, 3,216,000; white corpuscles, 30,600; lymphocytes,

SPECIMEN 1



The small, round cells are separated by a fair amount of stroma. Occasional large irregular cells and many eosinophiles, six of which are present in this field.

SPECIMEN 2



Practically all small lymphoid cells, showing a very great number of mitotic figures.

91.4 per cent.; polynuclear neutrophiles, 8 per cent.; eosinophiles, 0.4 per cent.; mast-cells, 0.2 per cent. The blood showed the usual changes of severe secondary anemia. Forty-seven normoblasts and 24 megaloblasts were seen while counting 400 white cells.

The diagnosis of lymphatic leukemia was then made on account of the high percentage of lymphocytes, in spite of the comparatively low white count.

A gland was removed from the left side of the neck by Dr. H. L. Burrell on October 17th. The examination of this tissue showed little resemblance to a normal gland. No follicles could be distinguished and the tissue was nearly uniform throughout the section. With the high power (magnification 900 diameters) there was seen to be a very great proliferation of lymphoid cells. These cells were not of the type of the usual small lymphocytes, but had the characteristics of the cells in the germ centres of the follicles and other places where there is active proliferation of lymphoid tissue. These cells had fairly large vesicular nuclei and showed enormous numbers of mitotic figures. In the greater part of the tissue there were no other cells. There was very little stroma, and in large areas there was none at all to be seen.

The larger cells, similar to those seen in lymphosarcoma, were absent. There were only occasional eosinophiles. There were numbers of nucleated red blood corpuscles in the sinuses.

A diagnosis of anemia associated with lymphatic hyperplasia, or acute lymphatic leukemia, was made from this examination.

All the sections in this case were studied with eosin and Unna's polychrome methylene-blue stain. Several sections from each specimen were also stained and examined for tubercle bacilli, but none were found.

Failure was progressive from this time on. There was a steady increase in the size of the lymph nodes, with progressive failure in the general condition and in the color of the skin and mucous membranes. The signs of new-growth in the chest did not increase a great deal, but respiration continued difficult. There were no further hemorrhages. The nasal discharge diminished during the last two weeks. The urine was always normal. The hemoglobin and the number of red corpuscles diminished steadily,

while the number of white corpuscles increased, reaching 174,600 the day before death, which occurred on November 4th, five months after the onset. The percentage of mononuclear cells remained high, varying, however, at different examinations. The results of the later examinations are shown in the table. An autopsy was refused.

Date.	Hemoglobin.	Red corpuscles.	White corpuscles.	Small mononuclear.	Large mononuclear.	Polynuclear neutrophiles.	Eosinophiles.	Myelocytes.	Mast-cells.	To 400 whites: Microblasts.	To 400 whites: Normoblasts.	To 400 whites: Megaloblasts.	Polychromatophilia.	Variation in size.	Poikilocytosis.	Stippling.
	%			%	%	%	%	%	%							
Aug. 23	45	2,080,000	16,200													
" 31	40	1,765,000	19,000	58.0	9.0	32.8	0.2	.....	.....	2	13	22	None	Consid.	Mod.	?
Sept. 16	70	4,800,000	29,200	56.0	16.0	24.8	0.2	2.0	1.0	...	26	12	Mod.	Consid.	Consid.	slight
" 30	70	4,200,000	34,000	50.0	12.0	34.0	1.0	2.5	0.5	...	21	5	Consid.	Mod.	Mod.	slight
Oct. 10	55	3,216,000	30,600	91.4		8.0	0.4	.....	0.2	...	47	24	Usual changes of severe secondary anemia.			
" 20	...	.....	.....	58.6	27.7	11.7	1.0	1.0								
" 25	25	2,960,000	49,000	48.0	28.0	20.0	.....	2.0	2.0	...	4	12	Mod.	Mod.		
Nov. 3	20	.....	174,600	72.5	17.5	6.0	.....	4.0	.....	...	6	18				

The case is of interest in that it afforded an opportunity to study the development of the changes in the blood and lymph nodes during a considerable period, and that, although it was most carefully studied, the correct diagnosis could not be made until a comparatively short time before death. It is unfortunate that the picture could not have been completed and the diagnosis still further verified by autopsy. It shows, however, that the character of the changes in the blood may not develop to a degree sufficient to justify a positive diagnosis for many months. It also shows that the changes in the lymph nodes may be, not only at first, but even for a considerable time, materially different from those which are usually considered to be typical of this disease. It is noteworthy that the characteristic changes in the blood and lymph nodes appeared at essentially the same time.

The only inference that can be made from the histologic study of these tissues at different stages of the disease is that lymphatic

leukemia may have its origin in a malignant growth affecting the lymphoid tissues more or less generally, and that not until there is a secondary proliferation of the lymphoid cells do we get the typical tissue picture and blood condition which is characteristic of lymphatic leukemia. It suggests that leukemia, pseudoleukemia and malignant lymphoma cannot be separated as three distinct entities, and that they do not always differ characteristically in the histologic structure of their lymphoid tissues, and that the microscopic sections in these cases will be often wrongly judged in the absence of complete clinical data as regards the distribution of the process and the examination of the blood.

In short, this case emphasizes again our ignorance as to the development of the pathologic changes in the diseases of the blood and lymph nodes. It does not warrant any definite conclusions, either specific or general, but is reported simply as a contribution to the literature of these subjects with the hope that it may be of some assistance in the solution of the problems connected with them.

A CASE OF LYMPHATIC LEUKEMIA.

By F. FORCHHEIMER, M.D.,
OF CINCINNATI.

I saw this patient in consultation with Dr. R. W. Stewart, by whose courtesy I am permitted to report it. The origin of the disease and the remarkably high lymphocyte count made it of great interest:

The patient, a healthy child, at the age of eight months had an attack of follicular angina, produced by a mild infection of streptococci and staphylococci. One month after this, swelling of both parotids began; also of the posterior lymphatic glands. It was supposed that this was an attack of mumps, the maximum temperature being 101°. Ten days after this the same symptoms persisted.

On December 9, 1904, the submaxillary glands were also enlarged.

10*th*. A blood count gave the following: leukocytes, 90,000; small lymphocytes, 96 per cent.; large lymphocytes, 0.8 per cent.; polynuclears, 3.2 per cent.; normoblasts, 0.7 per cent.; gigantoblasts, 0.2 per cent; beginning poikilocytosis.

11*th*. The child's condition was poor; examination showed liver dulness somewhat increased. The spleen could not be palpated, although there was increased dulness in the region of the spleen. The inguinal glands were enlarged.

12*th*. The blood examination showed the following: reds, 3,900,000; whites, 82,400; hemoglobin, 70 per cent.; lymphocytes, 97.6 per cent.; polynuclears, 2.2 per cent.; eosinophiles, 0.2 per cent. No normoblasts but a few gigantoblasts were found. The lymphocytosis was due to increase in the small and intermediate forms; there were a few unusually large lymphocytes with faulty staining properties. One mast-cell and one eosinophilic myelocyte were found. The red cells stained well, but the coagulability of the blood seemed diminished.

13*th*. The anterior margin of the spleen could be felt.

14*th*. The urine showed a little albumin. Microscopically, nothing.

18*th*. Splenic enlargement well marked, axillary glands beginning to be enlarged. A blood examination, ten days after the first one was made, gave the following: reds, 3,300,000; whites, 88,800; hemoglobin, 35 per cent.;

small lymphocytes, 98 per cent.; large lymphocytes, 1 per cent.; polynuclears, 1 per cent.; eosinophiles, 0 per cent.; normoblasts, 2; gigantoblasts, 3. The child was now beginning to become pale.

20*th*. I saw the child and found the conditions as described, both liver and spleen being enlarged; the latter not markedly so.

21*st*. There was decided improvement; the glands were smaller; but there were a few purpuric spots on the posterior aspect of the right leg just above the knee-joint. In the evening there was a slight epistaxis.

23*d*. Some diarrhea; marked sweating. Up to this time appetite remained undisturbed. A blood count now reveals the following: reds, 3,240,000; whites, 151,000; hemoglobin, 35 per cent.; small lymphocytes, 99.6 per cent.; large lymphocytes, 0 per cent.; polynuclears, 0.4 per cent.; eosinophiles, 0 per cent. Otherwise no change.

The condition remains the same, except that epistaxis returns, but the appetite begins to diminish. The temperature does not exceed 100.4°. Crystals of uric acid were found in the urine.

From now on the epistaxis becomes uncontrollable. The child loses strength; it does not sleep. It vomits blood, the heart gets weaker, and the patient dies on January 2, 1905. The case ended fatally in less than ten weeks after the tonsillar attack, and in less than six weeks after the onset of the glandular symptoms. At the time of death every gland that could be felt was enlarged.

DISCUSSION.

Dr. Barker: I should like to ask Dr. Morse if he regards the increase and the histologic changes in the lymphocyte in the blood permits him to decide that these lymphocytes are derived from the lymph glands? If the evidence is sufficient it would be an important observation, for the tendency has been growing lately to consider every case of lymphatic leukemia as myelogenous in origin. It has been supposed that marked increase in the number of the lymphocytes in soft organs, like the lymph glands and the spleen, may occur without any increase in the lymphocytes of the blood. But when proliferation occurs in the white cells in the marrow the limit to expansibility is given by the bony capsule, and it is owing to this limit it has been supposed that the cells come out into the blood. I feel very uncertain as to the validity of this modern theory, though it must be admitted that it is plausible. I have been working on a case of lymphatic leukemia recently in which there was no marked alteration in the lymph glands, and have been especially interested in this side of the problem. The other question I should like to ask Dr. Morse is whether or not he regards the blood in the spaces in the lymph gland he described as hemorrhage into a lymph gland, or was it due to the extraction of a hemolymph gland for examination? In the case of lymphatic leukemia

I am studying there were some supposed lymph glands saved from the retroperitoneal region, but on examining them they are apparently Wharton's hemolymph glands.

Dr. Thayer: I remember two cases similar to that under discussion—cases which in the beginning showed glandular enlargement suggestive of Hodgkin's disease, with but little anemia, the blood showing nothing characteristic excepting a rather large relative proportion of the smaller form of lymphocytes. Later on, however, there developed the characteristic blood picture of small-celled lymphatic leukemia. Both of these instances were in adults.

Dr. Welch: I agree with Dr. Barker in reference to the great interest attaching to the histologic study of the lymphatic glands in this class of cases. I understand that the first might be Hodgkin's disease. Everybody knows the great confusion which has always existed as to both classes of enlargements, tumors of the lymphatic glands. The multiplicity of terms shows how great the confusion is. It leads me to the conclusion that we can distinguish three by mere microscopic examination, three fairly histologic pictures, so we can feel tolerably sure that we can distinguish Hodgkin's disease from lymphoma associated with leukemia; and in going into the points which enable one to make these distinctions I call the attention of those who have the opportunity to the great importance of making pretty careful histologic examinations in reference to the points distinguishing Hodgkin's disease from lymphoma associated with lymphatic leukemia and sarcoma. I think the term lymphosarcoma should be abandoned altogether.

Dr. Morse: I had hoped that Dr. Low would be able to come to the meeting to demonstrate the specimens and discuss the pathologic side. I do not feel competent to answer Dr. Barker's first question. I don't know. The glands were not hemolymph glands. As to Dr. Welch's question, while I cannot speak authoritatively, my impression is that the pathologists in Boston are not as ready to admit the existence of a specific picture of Hodgkin's disease as are those in other cities.

A BRIEF REPORT ON RESEARCH IN THE WRITER'S LABORATORY ON BACTERIAL TOXINS AND IMMUNITY.

By VICTOR C. VAUGHAN, M.D.,
OF ANN ARBOR, MICH.

THEORY. The research on the action of toxicogenic bacteria and the production of immunity that has been prosecuted for some years under my direction is based upon a theory different, in some respects, at least, from any held by others, so far as I know. I believe that the bacterial cell, so far as its essential constituents are concerned, is a definite chemical compound, just as much so as is sodium chlorid or phenylhydrazin, but of course infinitely more complex. The number of groups in these large molecules must be great, and when such a molecule is broken up the lines along which cleavage takes place depend upon the nature and degree of the force applied. All life is cellular, and every cell is in its essential constituents a definite chemical compound. Cell growth is a chemical process. There can be no chemical element in any cell which did not pre-exist in the medium in which the cell grows; but the arrangement of the chemical elements in the cell may be quite different from that in the medium. Some bacterial cells, like the colon bacillus, may take the elements as they exist in relatively simple compounds and build them into their own bodies. These organisms grow in proteid-free medium. Other bacteria, such as the typhoid bacillus, require, as it were, ready-made atomic groups, and consequently will not grow in mediums which do not contain proteid bodies.

The cell molecule, even that of a bacterial cell, must be exceedingly complex, consisting of a great number and variety of atomic groups. Certain of these groups are undoubtedly common to many kinds of cells, but each species of cell must differ from

all others somewhere in its molecular structure; certain atomic groups must be absent in one and present in the other, or the arrangement of the groups with reference to one another must vary. Some atomic groups are loosely held in the molecule and drop off from time to time, to be replaced by similar groups built up from the constituents of the medium in which the cell lives. These groups that drop off from the cell molecule constitute its secretions, and it seems to be the chief function of certain cells to form these easily detachable groups, which go to serve other cells, in some instances beneficially, in others harmfully. Other atomic groups are held in the cell molecule more closely, and cannot be split off without destroying the cell itself.

Every toxicogenic bacterial cell must have among its constituent groups at least one which is poisonous to certain animals. Some toxicogenic bacterial cells have poisonous groups that are easily detachable, and the cell continues to reproduce this poison. In this case we may say that the bacterial cell secretes a poison. This is true of the diphtheria and tetanus bacilli. In other toxicogenic bacteria the poisonous group is not set free until the cell molecule is so thoroughly broken up that the life of the cell is destroyed. To this group most of the pathogenic bacteria belong. From bacteria of this class the poisonous group of the cell molecule cannot be extracted by physical solvents, but may be separated from other constituent groups of the cell molecule by chemically breaking up the cell.

When bacterial cells of the second class die their cell molecules break up into their constituent groups, and the poisonous, as well as the non-poisonous, groups are set free. This process is known as cell autolysis, and accounts for the appearance of soluble poisons in old cultures and in emulsions of bacteria kept for a while at relatively high temperatures.

When an animal is infected with bacteria of the second class the bacterial poison is not set free until the cell molecule is broken up. When the bacterial poison is set free it acts injuriously on the animal by entering into a chemical reaction with the constituent molecules of certain body cells. The bacterial poison, having a greater affinity for some constituent of the body cell than that which holds this particular group in its place, combines with it and thus impairs the function of that body cell. The injury

done to the animal as a whole depends upon the number and kind of body cells thus put out of commission. If the body cells impaired by the bacterial poison belong to some vital group, such as the respiratory centre, a relatively slight injury may immediately put the life of the animal in jeopardy; while, on the other hand, if the body cells affected are blood corpuscles, either white or red, or liver or kidney cells, more extensive injury may be done without any immediate and recognizable effect upon the health of the animal. Like other poisons, those derived from bacterial disintegration have what we call a selective action, which, I take it, depends upon the relative chemism existing between them and the constituents of certain body cells.

My theory can probably be better illustrated by the following diagrams:

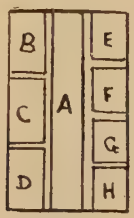


Fig 1.

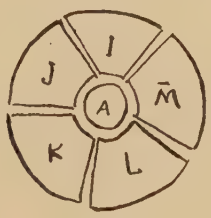


Fig.2.

FIG. 1.—A, nuclein group; B, amido group; C, diamido group; D, monoamido group; E, toxic group; F, hemolytic group; G, hemoglobin splitting group; H, carbohydrate group.
FIG. 2.—Body cell.

Suppose that the chemical attraction between group "e" in the bacillus molecules and group "m" in the cell molecules is greater than that which holds these groups in their respective molecules; then these groups will be broken away from their molecules and unite to form a new molecule, which, being saturated and stable, is not harmful. The body cell, injured by the loss of its "m" group, will have its function impaired more or less, depending upon the functionating value of that particular group to the cell. If the "m" group is essential to continued existence of the body cell, that cell is destroyed by the removal of the "m" group and repair is impossible; if, on the other hand, the body cell can continue its existence after the loss of the "m" group, the injury done is repaired by the cell splitting off

new "m" groups from the food material within the range of its chemism. In doing this it splits off more "m" groups than it can utilize, and this excess becomes the antitoxin or the bacteriolytic or hemolytic body, as the case may be.

This attempt to illustrate the theory diagrammatically, while of possible value, is to a certain extent misleading. I have no idea that the reaction between bacterial cell and body cell is as direct as the diagrammatic explanation indicates. There may be many intermediate reactions before a bacterial cell placed in the abdominal cavity can impair the function of a body cell in the respiratory centre of the brain. However, if by chemical means we can split up the bacterial cell outside the animal body and then inject the free toxic group into the animal, we should get the effect of the poison within a relatively short time; and this is exactly what we have attempted, and, in my opinion, have succeeded in doing.

Chemistry of the Bacterial Cell. In attempting to work out the theory, briefly and inadequately stated above, the first thing to do is to obtain the cell substance in large amount and free from all substances that do not form a part of the cell molecule. The tanks which I first described before this Association have enabled me to obtain the cellular substance of certain bacteria in large amount, and this has been freed from everything except that held in chemical combination by subjecting it to thorough extraction with such solvents as water, dilute saline solutions, ethyl and methyl alcohol, ether, chloroform and benzol. Practically, however, we have found that the only solvents needed for the extraction of the cell substance are dilute salt solution, alcohol and ether, and in our routine work only these are used. By carrying the cellular substance of the colon bacillus through these extraction processes, pulverizing and passing it through the finest sieve, there is obtained an impalpable white powder which, under the microscope, still shows the individual bacilli, and these take the ordinary stains. This powder is designated as the "crude toxin." It kills all guinea-pigs when suspended in salt solution and injected intra-abdominally in the proportion of 1 to 40,000 of body weight. This substance, when heated at 78° in a reflux condenser, with from fifteen to twenty-five times its weight of a 2 per cent. solution of pure sodium hydroxid in

absolute alcohol, is split up into portions A and B. Three extractions of an hour each are necessary in order to make this cleavage complete. After this treatment portion A is in solution in the alcohol and portion B is in the residue.

The alcoholic solution of A is neutralized by the addition of hydrochloric acid, an excess of the acid being avoided by preliminary titration of an aliquot part. When this is done the sodium chlorid is precipitated, removed by filtration, and the filtrate evaporated *in vacuo* at 40°. The residue is easily reduced to a brownish powder. This is known as the "crude soluble toxin;" crude, because it is still a mixture, and soluble, in contradistinction to the germ substance. It is freely soluble in water, ethyl and methyl alcohol, insoluble in ether, chloroform and benzol. Its aqueous solutions respond to all the proteid color reactions with the exception of that of Molisch. There is no evidence that this substance contains an alkaloidal body; at least, all attempts to extract an alkaloid have proven fruitless. The poisonous constituent of portion A is precipitated by platinum chlorid, but we have not been able to obtain the platinum compound in crystalline form. On account of its toxicologic action we suspect that portion A contains a neurin group, but up to the present time we have not been able to prove the presence of neurin chemically. The action of portion A on animals will be discussed later, and more detailed information concerning its chemistry may be found in a recent paper from my laboratory by Dr. Wheeler.[1]

It is well to state that the method which we have employed of splitting off the poisonous group from the cell molecule of the colon bacillus is by no means perfect, and, indeed, it leaves much to be desired. In the first place it is expensive, on account of the large amounts of absolute alcohol and ether, especially of the former, required. In the second place a large proportion of the toxic group—about three-fourths of it—is broken up by the reagents employed. The great loss may be better shown by the statement that from a "crude toxin," 10 mg. of which killed guinea-pigs, we obtained a "crude soluble toxin," 60 mg. of which was required to have the same effect; and yet the "crude

[1] Journal of the American Medical Association, April 22, 1905.

soluble toxin" was only about a third of the "crude toxin," which was split up, and the residue, equivalent to two-thirds of the "crude toxin," was shown by animal experiment to have no toxin left in it. It is possible that methyl alcohol may be advantageously used, but in our work we have purposely avoided it on account of its toxic properties.

Portion B, the part insoluble in absolute alcohol, is placed in a Soxhlet and thoroughly extracted with absolute alcohol in order to remove the alkali. After this treatment portion B is found to be, for the most part, soluble in water, forming a feebly alkalin solution. When this is rendered acid by the addition of hydrochloric acid a flocculent precipitate forms and is collected by the centrifuge and removed by filtration. This part, known as the acid precipitate from portion B, gives the proteid reactions, but has not been closely studied and will not receive further notice in this paper. The filtrate from this acid precipitate gives, on being heated, a second precipitate, and this is of interest, inasmuch as it contains a hemolytic body. This will receive further mention later.

Action of the Crude Soluble Toxin. It is interesting to compare the effects of the living colon bacillus, the dead germ substance, or, as we have called it, the "crude toxin," and the crude soluble toxin on animals. When a fatal quantity of a colon culture is injected intra-abdominally in a guinea-pig the animal remains apparently normal for a period of from eight hours to twelve hours, varying with the virulence and amount of the culture employed. During this time the animal eats, its coat is smooth and natural, and its temperature is normal or possibly slightly above. At the expiration of this time the pig begins to show it is sick. It sits in one corner of the cage, its coat becomes rough, and its temperature begins to fall, and continues to do so until death, which occurs within twenty-four hours. When the dead germ substance, or "crude toxin," is injected in fatal quantity the effects are exactly the same as with the living bacillus, except that the period between the giving of the toxin and the first appearance of sickness is shorter; the temperature beginning to fall within from two to four hours continues to fall until death, which occurs within twelve hours. The postmortem appearances, the most marked of which is a hemorrhagic peritonitis, are the

same, whether the living or dead germ be used. There can, therefore, be no doubt that the toxic substance, by virtue of which the living bacillus destroys the life of the pig, is present in the dead germ substance. With the "crude soluble toxin," or portion A, split off from the dead germ substance by a dilute alcoholic solution of sodium hydroxid the effect upon animals is exactly the same as with the living and dead germ substance, again with the exception that the time between the administration of the poison and the appearance of illness, best measured by fall in temperature, is still further shortened, coming on within from ten minutes to fifteen minutes and continuing until death, which occurs within an hour. There is no peritonitis after death from the crude soluble toxin, but when this toxin is combined with sodium bicarbonate or with certain non-poisonous organic substances and injected into the abdominal cavity a hemorrhagic peritonitis identical with that observed after the living or dead germ is observed. The temperature curves with the living culture, the dead germ substance, and the split-off toxins are the same, with the exception of the time when the fall begins.

The soluble toxin of the colon bacillus kills when injected intravenously within six to seven minutes; when given intra-abdominally or hypodermically, within an hour. The fatal doses for guinea-pigs are intravenously from 1 mg. to 15 mg.; intra-abdominally, from 8 mg. to 60 mg. The fatal dose when administered hypodermically is between twice and three times that required to kill when given intra-abdominally.

It kills apparently by its action on the respiratory centre, respiration ceasing a measurable time before the heart stops. We have poisoned with it guinea-pigs, rabbits, and a goat, the time and manner of death being the same in these animals, but, of course, larger doses being necessary to produce a fatal result in the larger animals. A more detailed discussion of the action of the soluble toxin has been given in a recent paper by Victor C. Vaughan, Jr.[1]

A similar poison to that obtained in soluble form from the colon bacillus, as described, may be prepared by the same method from egg-albumen and Witte's peptone. It is probable

[1] Journal of the American Medical Association, April 29, 1905.

that this group is a constituent of a large number of proteid bodies. Besides the colon bacillus we have obtained this soluble toxin from the typhoid and anthrax bacilli and from the micrococcus of pneumonia. We have shown that the colon bacillus can build up this poisonous group synthetically when grown on proteid-free culture mediums. This experiment has served a double purpose, inasmuch as it has enabled us to be certain that the toxic group, in this instance, at least, did not come from any proteid carried over from the culture medium. Agar does not contain this group, or, at least, this group cannot be split off from agar by the method which we have used. For this reason we have in our recent work inoculated our agar tanks with colon cultures grown in proteid-free mediums. The fact that this poisonous group is contained in the pepton and albumin molecule offers an explanation of the poisonous action of these substances when injected intraperitoneally, subcutaneously and intravenously in animals. It also offers a possible explanation of the fact, reported by several observers, that the injection of beef-tea and other albuminous fluids gives some increased immunity to certain pathogenic bacteria.

The Production of Active Immunity with the Split Products of the Colon Bacillus. 1. With portion A, or the "crude soluble toxin." By beginning with non-fatal doses and increasing these at intervals of a week we have been able to establish in guinea-pigs and rabbits some degree of tolerance for the "crude soluble toxin." After from six to eight weeks of this treatment the animals bear without harm intraperitoneal inoculation of from two to four times the minimum fatal dose of living culture of the colon bacillus. Indeed, an injection of an amount of the soluble toxin slightly less than the fatal quantity will enable the animal to withstand twice the fatal dose of the living culture given the next day. In making these experiments we used controls that received 5 per cent. solutions of salt solution and beef-tea, and found that these animals were not protected. This transient protection against the colon bacillus may be secured with the "crude soluble toxin" obtained from egg-albumen and peptone, as well as with that made from the colon bacillus itself. However, the immunity obtained by a single injection of the soluble toxin is transient, and less in degree than that secured by

repeated treatments at intervals of from five to seven days. From a close study of the temperature curves we are inclined, for the present, at least, to the opinion that the immunity obtained with the "crude soluble toxin", corresponds with natural immunity, or, in other words, it is simply an increase in the natural resistance possessed by the guinea-pig and rabbit to small inoculations with the colon bacillus, and that it may result from the toxic group split off from albumins and peptones. This immunity is, in our opinion, not specific.

2. With portion B, or that part of the cell molecule that remains after the toxic group has been split off. Portion B is, in the ordinary acceptation of the word, not poisonous. As much as 500 mg. of it may be thrown into the abdominal cavity of a guinea-pig, and twice this amount used in like manner in a rabbit without appreciable effect. The temperature remains unaffected, the animal loses but little, if any, in weight, and soon regains what it may lose, and is without roughened coat or other evidence of illness. However, that portion B is a cell poison we have good reason for believing. When repeated treatments with it are given the animal finally dies of marasmus; besides, as we shall see later, it leads to the development of a specific bacteriolytic body, and we can scarcely conceive of this being done without affecting certain cells of the body. We think that portions A and B furnish excellent illustrations of two kinds of poison, the difference being due to the difference in the body cells acted upon. There is no doubt about the poisonous action of A. In sufficient doses, which are small, it kills animals within a few minutes. We have seen a large goat in convulsions within thirty minutes after such an injection, its respiration cease within forty-five minutes, and its heart stop after five or ten minutes longer. The most careless observer will admit that portion A contains a poison, while he would probably deny that B is possessed of poisonous properties, and yet B probably impairs the function of more body cells than an equal weight of A. Portion A strikes the cells of the respiratory centre and the animal dies promptly. Portion B reacts with other cells, the impairment of which has no such direct effect upon the life of the animal.

Animals treated with successive doses of portion B bear intraperitoneal inoculations of from eight to ten times the minimum

fatal dose of the living culture of the colon bacillus, and this immunity is specific. It is not induced by the corresponding split products from albumin and peptone, and it is specific for the colon bacillus and does not protect against the typhoid bacillus.[1]

A Hemolytic Body in the Colon Bacillus. I have stated that there is a hemolytic body in portion B. This can be extracted from the precipitate obtained after acidifying an aqueous solution of B, removing the precipitate that forms and heating the solution. The hemolytic body in this precipitate is soluble in alcohol and ether. A hemolytic body, probably identical with this, can be obtained in large amount by evaporating either the absolute alcohol or the ether used in extracting the dead germ substance. This body is a fatty acid, and it dissolves red blood corpuscles, either as a free fatty acid or as a neutral soap. Whether or not an antibody can be produced with it in animals we are not prepared to say at the present time. The probabilities are that the hemolytic body is no part of the cell molecule, because only traces of it are found in portion B, while much larger quantities are present in the alcoholic and ether extracts. It may be a secretion or a by-product formed in building up the cell molecule from the constituents of the culture medium.

Agglutination not Produced by the Split Products. The blood serum of animals immunized with either portions A or B does not agglutinate the colon bacillus. We treated one goat with heated cultures of the colon bacillus, a second with portion A, and a third with portion B. The blood serum of the first only agglutinated the colon bacillus. We conclude from this that agglutination is due to the action of some easily detached group or secretion of the bacillus, and that it has no direct relation to immunity; in other words, our work confirms an early statement of Widal that agglutination is a reaction of infection and not of immunity. To the latter it is only incidental.

We are not ready to claim that immunity can be obtained by the methods mentioned to all the pathogenic bacteria that have

[1] A more detailed statement concerning the production of active immunity with the split products of the colon bacillus has been given in a paper by Victor Vaughan, Jr., read before the Association of American Pathologists and Bacteriologists, April 21, 1905, but not yet published.

intracellular toxins; in other words, we do not think we would be justified in claiming that we have established a general law that either portion A or portion B gives immunity to the bacteria from which they are derived. Each micro-organism must be studied individually, and there are *a priori* reasons for believing that each has its own peculiarities of chemical structure. The agent that splits the colon bacillus molecules into portions, each of which may be used in securing increased resistance to living cultures, may have quite a different effect upon other pathogenic bacteria. We have, as has been stated, split off toxic groups from the typhoid and anthrax bacilli and the micrococcus of pneumonia, and I might add that with the toxic group from the typhoid bacillus we have increased the resistance of guinea-pigs to this organism to the same extent that we have secured it to the colon bacillus, but with portion B we have not done enough work with any other bacteria to enable us to make any positive statements. The problem which we have before us, involving as it does the chemistry of the bacterial cell and the physiologic action of its constituent groups, is one the solution of which no one can hope to accomplish without the expenditure of much time and labor. It opens up an untrodden field of research, and its limits lie far beyond our range of vision. Cellular chemistry is as yet a *terra incognita*, and somewhere in it lie hidden the facts the discovery and application of which are to place medicine among the exact sciences.

Summary.

1. The theory upon which this work is based assumes that the bacterial cell is, in its essential part, a chemical compound made up of many groups.

2. The endeavor in this work has been to split up the cell molecule of the colon bacillus into its constituent groups and to study the physiologic action of these groups.

3. The result of the work has been to show: (*a*) That the colon bacillus, even when grown upon proteid-free mediums, contains a highly poisonous group, and that animals treated with repeated doses of this group have their resistance to living cul-

tures of the colon bacillus multiplied from two to four times; (*b*) that a group similar to that mentioned can be obtained from egg-albumen and peptone, and that animals treated with this also show increased resistance to the living bacillus; (*c*) that animals treated with successive doses of that portion of the colon cell left after the removal of the poisonous group acquire a specific immunity to the colon bacillus; (*d*) that the blood serum of animals treated with either the poisonous group or the non-poisonous group of the colon bacillus does not agglutinate the living colon bacillus; (*e*) that cultures of the colon bacillus contain a fatty acid which, either as a free fatty acid or as a neutral soap, dissolves red blood corpuscles.

DISCUSSION.

Dr. Welch: Dr. Vaughan's experiments are certainly very valuable and of very great interest, and undoubtedly shed a good deal of light upon certain problems of infection, but I question whether they are able to explain the phenomena of infection at present exclusively by application of what we know of toxins obtained by culture. Of course, the toxins, such as diphtheria antitoxins, are understood to produce the phenomena of the disease. We can obtain from other classes of bacteria substances which produce fever and which produce inflammation, and, as he stated, the same results can be obtained from other albumins, but the general characteristics and specific phenomena, such as the characteristic Peyer's patches, lesions of the bone-marrow or of the mesenteric glands in typhoid fever, are not obtained in cellular toxins, which are obtained from culture. So that I question whether at present we are justified in taking the position that the specific poisons which produce the characteristic phenomena of the disease are contained in large amount in the killed products or in the bacteria. I also believe that we must suppose that the bacteria inside of the body are capable of producing poisons which are not present in the bacteria in culture. There are many reasons, I believe, which lead to that conclusion from a pathologic study of infection, so that then it is also significant that we cannot produce a very substantial and infective culture immunity by killed cultures.

Dr. Vaughan has spoken of the high degree of immunity from this colon product taken on the whole with the killed typhoid fever bacillus; no doubt a measure of protection is secured in that way; it is not comparable to the

immunity produced in diphtheria or tetanus; whereas if, as we know we do in the case of vaccination in smallpox, that is a different thing, that is a substantial and enduring immunity. I find another difficulty in the view that we possess in the killed culture a general toxin which is responsible for the characteristic phenomena of disease, namely, that bacteria are harmful when dead. I have difficulty in accepting that theory of infection that it is the death of the bacteria in the body that does harm. I think the growth and vital activity of the bacteria in the body are responsible for the progress of the disease. I recognize, of course, the great value of these experiments of Dr. Vaughan's, and I am also of the opinion that none of the toxins which are found in this class of bacteria—killed cultures—altogether explain the most characteristic phenomena of disease. To explain, bacteria inside of the body produce toxins which are present only in a limited amount in the artificial culture.

Dr. Meltzer: I should like to ask Dr. Vaughan whether the produced poisonous principle is specific? Are they not specific in antitoxins; that is, I mean those antitoxins of the colon? Do they produce immunity also against the colon bacillus?

Dr. Vaughan: In answer to Dr. Meltzer's questions. The increased resistance produced by the poisonous principle is not specific. The non-poisonous portion produces the specific immunity. You cannot get this immunity with egg-albumen or peptone. If you immunize an animal to the colon bacillus, that animal is not immune to typhoid infection. The specific substance is a true haptophore. It is not poisonous.

In reply to Dr. Welch. He believes, as we all know, that these bacteria produce different substances in the animal body to what they produce in culture. With all due deference to Dr. Welch, I think his view is founded altogether on theoretical data without one iota of experimental evidence to substantiate it. That is my way of looking at it. I know that it is quite difficult for a man who has always been a morphologist to look at anything from a chemical standpoint, and I suppose I have just the same trouble in looking at this matter from the other standpoint. I believe that bacterial cells are living chemical compounds, and that they build up synthetically within themselves poisons just as the poppy produces opium.

Dr. Welch states that the immunity obtained by dead cultures is only transitory. The immunity which I have reported is different from that induced by dead cultures. I extract the poisonous group from the bacilli and then immunize with the non-poisonous part. One can inject into a guinea-pig $\frac{1}{2}$ gm. of the non-poisonous part of the colon bacillus, while 5 to 10 gm. of the whole germ substance would kill it.

There is nobody else who has ever attempted to get immunity by splitting up the germ cell chemically. My work is wholly different; different in concep-

tion and different in execution from that which has been done by McFayden. He is using nothing more nor less than finely pulverized germ substance. He has not chemically split up the cell substance. Sodium chlorid is not poisonous, but if you split it into sodium and hydrochloric acid then there are poisonous substances. I do not mean to say that all germs can be split up in just the same way. I have already made some preliminary experiments with the micrococcus of pneumonia, and in these preliminary experiments the residue apparently increases the susceptibility of the animal to the germ.

A CASE OF ACUTE LEUKEMIA, WITH SOME STRIKING CLINICAL FEATURES. OBSERVATIONS ON METABOLISM IN THIS CASE, AND IN A CASE OF SEVERE PURPURA HEMORRHAGICA.

By DAVID L. EDSALL, M.D.,
ASSISTANT PROFESSOR OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

My chief purpose in this report is to discuss certain disturbances of metabolism in leukemia and purpura hemorrhagica that are of much clinical and pathologic importance, and to inquire somewhat into the nature of these disturbances, particularly their relation to the hemorrhage that occurs in both these diseases. I shall, however, first mention briefly some striking clinical features in the case of acute leukemia, which are of interest from an etiologic, and particularly from a diagnostic, standpoint.

There was an apparent connection of the beginning of the symptoms with the extraction of a tooth, and therefore with the opportunity for infection, a point that is of some interest in relation to the etiology of the condition; and the clinical resemblance of the case to diphtheria and angina Ludovici has serious diagnostic importance. In this instance the possibility that the disease had originated from mouth infection set up through the extraction of a tooth must, however, be dismissed as extremely improbable. The very early appearance of severe stomatitis in many cases of acute leukemia has led to the repeated suggestion that the disease itself, or at least the rapidity of its progress, is caused by infection, particularly through the diseased mouth; and in a number of instances, as in my case, the extraction of a tooth was apparently directly followed by rapidly progressing acute leukemia. In the

instance that I am describing, however, the actual conditions were almost certainly the reverse of this; that is, the disease itself, in its incipient stage, evidently produced the symptoms that led to the extraction of the tooth.

As to the appearances suggesting diphtheria and angina Ludovici, there is, I think, in systematic writings dealing with acute leukemia, or in more fragmentary papers, little, if any, discussion of the possibility of mistaking this disease for diphtheria, and there is no sufficient consideration of the possibility of mistaking the disease for simple angina Ludovici without other general disorder. Late in the course of this case it would have been wholly impossible without bacteriologic investigation to have stated that it was not diphtheria; and, on the other hand, angina Ludovici seemed, when I first saw the man, to be probably the main condition present until the blood examination, that was made immediately afterward, showed at once that he had acute leukemia. In the classes in pathologic anatomy in the General Hospital at Vienna, specimens from several cases of acute leukemia have, I am told, been exhibited in recent years with the statement that they had been mistaken for some time for angina Ludovici. This mistake is a natural one, and could scarcely be avoided in some instances until the blood condition became distinctive. Indeed, there is every opportunity for patients with acute leukemia to develop actual Ludwig's angina, the condition of the mouth that is so common in this disease giving ready opportunity for infection of the tissues of the neck.

Without giving extensive details of the clinical side of the case of acute leukemia, I would refer to the following points: The patient, a man aged thirty-six years, was seen with Dr. Cryer on January 15, 1901. He gave a good family history, and a personal history that was of no interest until about three weeks before I saw him. For some months previous to this time he had been under severe business and emotional strain, but no results of any consequence had been noted. Late in December, 1900, the first symptoms of importance appeared. He then had swelling of the gum about the upper posterior molar tooth on the right side, together with much pain, and his dentist extracted the tooth. The fact of interest at this point is that the trouble with the tooth was almost

certainly due to leukemic infiltration of the tissues about it. The history first obtained from the patient apparently indicated the contrary—that the disease in the mouth and elsewhere had followed the extraction of the tooth, for subsequent to its extraction he had local ulceration of the gum, of unhealthy appearance and with necrotic pseudomembrane over its surface, and this ulceration advanced until it involved a large part of the surface of the gums of the left side of the mouth. At this period, too, the man noticed the first disturbance in his general health. The tooth, however, was healthy, and there was at that time no disease of the surrounding tissues, the necrosis having followed the extraction merely because of the disease that had already begun. It seems probable that had this point been ascertainable, it could have been shown in at least a considerable portion of the other similar cases in the literature that the initial symptoms of leukemic infiltration actually preceded the development of the local opportunities for infection.

Because of the dental condition the patient was seen in consultation by Dr. Cryer a week after the tooth was extracted, and ten days later than this, after a telephonic communication, Dr. Cryer had him admitted to the private ward of the University Hospital for examination, thinking that the condition of the mouth might be due to an impacted tooth. It was, however, at once apparent that he had serious general disease, and at Dr. Cryer's request I took charge of him. In the period intervening between this time and his previous visit to Dr. Cryer he stated that there had been marked and rapid loss of strength, with a good deal of emaciation and mental depression; and he had also had decided disturbance of vision and hearing, having had difficulty in reading even the large print of a newspaper, and at times in recognizing the members of his family, and having become so deaf as to be uncertain about ordinary conversation. For some days before entering the hospital he had had much pain on attempting to masticate or swallow, and had had a slight, thin, bloody discharge from the nose; he had also become extremely hoarse, and had had difficulty in inspiration. There had been no other noteworthy symptoms. At the first glance the immediate suggestion was that he had a severe diphtherial

infection. He was evidently much prostrated; the pulse was rapid and weak; he had marked inspiratory stridor, and his voice was a hoarse whisper; there was a thin, blood-tinged discharge from the nose; a little pseudomembrane was at once visible in the nose, and he evidently had distress upon swallowing. His temperature was 101.2°. General examination at once made the possibility of diphtheria very questionable; it showed the following conditions: He was weak and seemed emaciated; there were small ulcers, with hemorrhagic bases on the lips and about the nostrils; there was a narrow line of ulceration of the mucous membrane of the upper jaw, most marked posteriorly, but extending to the incisors; there were similar patches of ulceration on the lower jaw, though less extensive, and there were small ulcers beneath the tongue and on the dorsum of the tongue. All these ulcers had hemorrhagic bases, but were not bleeding. Their surfaces were covered with a dirty looking, yellowish-gray pseudomembrane-like necrotic deposit. The gums were swollen and congested, but did not bleed upon manipulation; the tongue was somewhat swollen. The pillars of the pharynx and the walls of the pharynx itself were very much swollen, and the tonsils were so large that there was a space of only half an inch between them. The lumen of the pharynx also seemed very small, as a result of the swelling of the tissues. There was, however, no redness, pseudomembrane formation, or ulceration back of the tongue. The nose was nearly blocked on both sides, the mucous membrane swollen and somewhat congested, and there were small ulcerated areas which showed a pseudomembranous deposit.

The man's neck appeared to be much swollen, particularly on the left side, and the tissues, on the left side especially, felt dense and infiltrated half-way down to the clavicle. Part of this was evidently due to glandular enlargement, one gland, about one and one-half inches in length, being readily felt, as well as a number that were smaller; but the swelling of the neck was so conspicuous as to be evident at the first glance, and it appeared to be due to a considerable extent to diffuse infiltration of the tissues, and not simply to glandular enlargement.

The glands elsewhere could be everywhere felt, and in the axilla several were about an inch in diameter; the spleen could not be

palpated, but the dulness was enlarged. Examination elsewhere showed nothing of diagnostic importance. The lungs were decidedly congested at the bases; the heart was a little dilated, the sounds weak, the action rapid. The man had difficulty in reading even the head lines of a newspaper, and he could hear a watch at but six inches distance with the left ear; three inches with the right.

A culture was taken at once, and proved negative for diphtheria bacilli. The resident physician's blood count, which was immediately confirmed by Dr. C. Y. White, showed 466,640 leukocytes; 1,820,000 red cells. The hemoglobin estimations at this time and subsequently were unreliable because of the immediate clouding that took place.

The examination of stained specimens showed a very definite but somewhat peculiar picture of acute lymphatic leukemia. I shall not discuss the morphology of the blood, as I have asked Dr. White to include the study of this blood in discussing a series of cases that he is collecting.

The conditions that I have mentioned show that there was a strong suggestion of diphtheria and also of angina Ludovici in the case. Twenty-four hours after I first saw him diphtheria could certainly not have been excluded without negative cultures; even the definite determination that acute leukemia was present would scarcely have finally excluded diphtheria, for at that time he had pseudomembrane on both tonsils, and he had the nasal and laryngeal symptoms that are so common in diphtheria.

The further progress of the case was one of increasing prostration, with death two days and a half after I first saw him, from cardiac failure, edema of the lungs, and sudden collapse. The course was interesting in only two particulars: In the first place, the obstruction of his larynx grew more and more severe, and finally became so marked that the possible necessity for tracheotomy was kept anxiously in view, though this measure would have been most reluctantly undertaken because of the hemorrhagic tendency. So far as I know, marked laryngeal obstruction has not been described in acute leukemia, though it has repeatedly been seen in chronic lymphatic leukemia. The laryngeal symptoms were, as was expected, found to be due to extensive infiltration

of the larynx, with marked swelling and slight ulceration of both the false and the true vocal cords.

The other point of interest was the hemorrhage. The man exhibited no hemorrhagic tendency, excepting as a result of the second puncture made for study of his blood. This minute wound was followed by oozing of blood in almost a continuous stream for the greater part of an hour; all measures used to stop it were ineffectual, and the amount of blood lost was certainly as much as a pint. This feature is interesting chiefly in relation to the manner in which the hemorrhage was produced. Grave hemorrhage from the same cause has previously been described in rare instances.

A few hours after his admission, when the diagnosis of acute leukemia had been made, a metabolism experiment was begun. This, unfortunately, could be continued for but one period of twenty-four hours, because it became impossible after this to save his urine, owing to his profound prostration and mental obscurity. In this time, however, sufficiently characteristic conditions were observed.

He took during this period only milk and broth. The nitrogen content and the amount of P_2O_5 in these were determined. I also determined the nitrogen and P_2O_5 in the urine: estimations of the uric acid and purin bases were begun, but, unfortunately, were lost through the mistake of a laboratory servant.

The man's food contained 7.25 gm. of nitrogen, 1.84 gm. of P_2O_5. The urine during the same period contained 29.534 gm. of nitrogen and 3.056 gm. of P_2O_5. While I lost the estimations of uric acid and purin bases, I think I am safe in saying, from the large precipitate produced by ammoniac silver nitrate, that the uric acid was greatly increased; it was probably above 2 gm., at any rate. The feces could not be accurately collected, and hence the nitrogen and phosphates in the feces were not determined; there was probably more than 1 gm. of nitrogen in the feces, however. In addition to this, the man lost during this period, as I have stated, a large amount of blood, and this must have contained 4 gm. or more of nitrogen. The balance between the intake of nitrogen and the outgo in the urine alone shows a loss of 22.28 gm., and with the loss from other sources he must in all have had a negative nitrogen balance during this twenty-four hours of as much as 27 gm.

The loss of phosphorus, while decided, was not so remarkable as the loss of nitrogen. It was probably over 2 gm.

Such tremendous tissue destruction is a condition that is comparatively rare in other diseases, but it seems to be very common in acute leukemia, as far as the very few chemical investigations of this disease that are on record indicate. It appears, therefore, to be a very important element in the pathology of the condition. Magnus-Levy, in particular, directed attention to this very remarkable disturbance of metabolism, reporting his own results in three cases, in one of which he determined the nitrogen of the urine, and in the other two the actual balance between the intake and the outgo. In the first of his cases there was a loss in forty hours by the urine alone of 24.8 gm. more than the patient had taken in his food. In addition to that, he lost 3 gm. in the feces and about 17 gm. by hemorrhage, so that in all this patient showed in a period of forty hours a negative balance of nearly 45 gm. of nitrogen. In the second case 85.4 gm. of nitrogen were lost in seven days, and on the last day there was a negative balance of 20.8 gm. In the third case, with a very low food intake, the urinary nitrogen averaged 21 gm. during the last seven days, and on one day the nitrogen excretion in the urine rose to 27 gm.

A similarly marked loss was evidently present in Ebstein's case, in which over 62 gm. of urea were found in the twenty-four hours' urine, and a number of other authors have seen much the same state of affairs. It is of interest that in Wey's case of chronic leukemia, with a terminal very acute stage, the patient passed per day as much as 29 gm. of nitrogen in the urine. This violent disturbance is apparently not an essential part of the pathology of acute leukemia, as there are one or two reliable cases on record that showed no marked loss; nevertheless, it appears from the observations that have been made to be a very pronounced and common feature.

Since leukemia is a disease chiefly of the lymphatic glands and bone-marrow, it is but natural that the metabolism of the nucleins should show most striking evidence of disturbance. The excretion of uric acid and phosphates has been found very excessive in most cases, and some of the figures obtained by Magnus-Levy were exceed-

ingly remarkable. One of his cases showed a loss of about 15 gm. of P_2O_5 in fifteen hours, a most astonishing figure; and in the same case the uric acid excretion reached 12.22 gm., which, considering this patient's low food intake, was certainly twenty times the normal amount, while the purin bases were 0.321 gm. Similar, though less striking, losses have been observed by others. Wende, for example, reported a case in which the uric acid excretion reached nearly 5 gm. There are, however, a few cases on record in which the uric acid excretion was very slightly, if at all, increased.

It is a matter of great clinical interest, as well as pathologic, to attempt to determine the cause of this profound disturbance of metabolism. Magnus-Levy, because of his own observations on nitrogen metabolism in hemorrhagic disorders, particularly in a case of purpura hemorrhagica, and because of a few observations of other investigators on the relation of hemorrhage to destructive changes in metabolism, reaches the conclusion that a large part, at any rate, of the tissue destruction in acute leukemia is probably dependent upon the hemorrhages that occur in this disease. This seems to me to be very questionable. Magnus-Levy's work, and that to which he refers, has shown to be sure that hemorrhagic conditions are often associated with a marked nitrogen loss, and it is not improbable that a small amount of tissue destruction is dependent upon the hemorrhage itself. The experimental work of Hawk and Gies, for example, in which the only abnormality present was loss of blood, shows that mere hemorrhage does produce some tissue destruction. But in such experimental work, in which other abnormalities are not present, hemorrhage seems to cause but slight disorder of general metabolism, and hence it would appear to be an insufficient explanation of the extremely unusual conditions found in acute leukemia. Furthermore, there are many cases of extensive purpura in which, even in the absence of accurate chemical investigations, the clinical appearances are such as to indicate pretty clearly that there cannot be in all cases a marked tissue loss. Therefore, since very severe abnormalities, besides the hemorrhage, are present in acute leukemia, it seems to me that hemorrhage offers a very incomplete explanation of the metabolic disturbance in this disease. Violent acute disturbance of metabolism is usually

due to some form of toxemia, and it would appear more rational to look to such a cause in acute leukemia than to attribute the major portion of the disturbance to hemorrhage; in other words, I should be prepared to learn that the hemorrhage and the disorder of metabolism were due to a common cause, probably a toxemia.

The conditions in the case of purpura hemorrhagica that I shall at once mention indicate very strongly, I think, that while some tissue destruction occurred in this case also, hemorrhage was not the cause of it; and hence I believe that this case goes far to remove the basis of Magnus-Levy's hypothesis that hemorrhage is the main cause of the tissue destruction in acute leukemia.

This patient was a boy aged sixteen years; he was admitted to the University Hospital on Dr. Musser's service December 15, 1904. Admission No. 3531. His trouble had begun eleven days before, with moderate joint pains, which had continued, but had not been severe at any time. There had been little swelling of the joints. Nine days before he was admitted to the hospital hemorrhagic spots had appeared in his skin; these had rapidly increased two days before his admission, and he had also had nausea and vomiting and cramping abdominal pain. The symptoms had become still worse on the following day. When admitted he looked very ill. He had nausea, frequent vomiting, and bloody bowel movements, and showed extensive subcutaneous hemorrhages, particularly on the arms and back. The symptoms continued severe, and on the 20th he was greatly prostrated and delirious, and his hemorrhages had increased to a most striking extent. I have never seen more widespread subcutaneous hemorrhages; they involved almost all the surface of the back, the arms and much of the forearms; there were large extravasations in the skin over the front of the chest and abdomen, many large patches on the legs and a number on the face. There were also small hemorrhages into the conjunctiva; he had hemorrhages from the mouth and nose; he vomited some blood, and he also passed blood from the bowel and with the urine. I began with this day (*i. e.*, urine of 20th and 21st, marked 21st in table) observations of his excretion of nitrogen, phosphates and uric acid. The excretion on the first two days represents total loss, as the patient was taking no food at this time; he was, indeed, losing

more than is indicated by the urine, as he was vomiting almost constantly. It was also impossible on the 27th and 28th to estimate the intake accurately, as he had severe vomiting much of the time.

It should be noted that on December 21st he was still having hemorrhages, was vomiting violently and was generally prostrated; on the 22d he was still very ill, but his gastric symptoms had, temporarily, largely subsided, and hemorrhage had, so far as could be determined, stopped entirely; on the 23d nearly all marked symptoms had ceased, and on the 24th he felt so well that I temporarily stopped my observations, as his attack seemed to be over. The point of chief interest is, however, that on the evening of the 24th he had a return of his gastric symptoms and on the 26th the joint pains, abdominal pain, gastric symptoms and prostration returned, but he had no discoverable return of hemorrhage. Observations of metabolism were again begun on this day. These symptoms lasted two days, and then decreased. Subsequently, though he had the signs of an acute nephritis, he improved with great rapidity in his general condition, and gained eleven pounds in a week. The figures for January 3d and 4th, therefore, represent his condition during convalescence. At this time he was getting between 11 and 12 gm. of nitrogen in his food. In the preceding periods, when he took food at all, he was probably getting at most 3 or 4 gm. of nitrogen.

Date.	Urine.	Nitrogen.	Uric acid.	P_2O_5.
December 21	1800	22.478	0.196	6.192
" 22	1700	23.738	Lost	4.012
" 23	1350	18.295	0.178	2.484
" 24	870	14.323	0.158	1.531
Return of symptoms, but no hemorrhage :				
December 27	1560	22.579	.....	2.280
" 28	1470	20.580	.....	1.705
Convalescent :				
January 3	880	6.718	.....	0.950
" 4	1275	6.642	.....	0.918

For the first two days these figures show, as far as the nitrogen and P_2O_5 are concerned, conditions that are very similar to those in my case of acute leukemia, and in the majority of the other cases in which metabolism has been observed, namely, a profound

loss. The next day, when there was no hemorrhage and the symptoms were all disappearing, there was a very marked decrease in the nitrogen and P_2O_5 loss, while on the fourth day the conditions were approaching the normal. The first four days, therefore, apparently support Magnus-Levy's view that the hemorrhage may be responsible for much of the metabolic disturbance. The conditions on the 27th and 28th, however, indicate directly the contrary. At this period hemorrhage was absent, but the renewed metabolic disturbance was only slightly less severe than that at the time when hemorrhage was occurring in wide areas, from the mucous membranes and into the skin. The conditions on January 3d and 4th are those to be expected in a convalescent; the man was, as his weight indicated, showing a marked retention, and he was evidently using this in building up tissue.

One case does not, of course, prove or disprove an hypothesis. Nevertheless, the conditions in this case; the fact that extensive hemorrhage often occurs without the clinical appearance of tissue loss; the knowledge that hemorrhage does not necessarily occur in acute leukemia; and the fact that, besides the hemorrhages, evidences of grave disorders of other kinds are present in acute leukemia and in many other hemorrhagic cases: all these unite, I think, to make it appear extremely improbable that the tissue loss should be attributed in considerable extent to the hemorrhage, and indicate, on the contrary, that the cause of both hemorrhage and tissue loss must be sought together in the nature of the disturbance that produces the disease.

At the time that I observed my case of acute leukemia I suggested that it is probable that the tremendous tissue loss is due to some pathologic disturbance of autolytic processes. This suggestion was at that time almost a pure hypothesis, but the hypothesis was based upon the fact that similar metabolic conditions are seen in pneumonia at the time of the crisis, and in acute yellow atrophy of the liver; and in these diseases sudden and very extensive autolytic tissue destruction occurs; in the lung exudate in the one case, in the liver in the other. Since that time further experiment has led physiologists and pathologists to a general acceptance of the importance of autolysis in a great number of physiologic and

pathologic conditions, and the suggestion that the metabolic disturbance in acute leukemia is a disturbance of autolysis is on general grounds now better justified.

More direct evidence in favor of this view is found, I think, in observations that I have recently made on the influence of the *x*-ray on metabolism in chronic leukemia.[1] In a case successfully treated there was, immediately upon the use of the *x*-ray, a most astonishing increase in the excretion of nitrogen, uric acid, purin bases, and P_2O_5. The excretion was, on the whole, fully doubled and that of uric acid, purin bases and P_2O_5 was ultimately much more than doubled. On the other hand, a case of chronic leukemia that was unsuccessfully treated with the *x*-ray showed almost no change in metabolism as a result of this treatment, and soon died, with constantly decreasing excretion. The fact that normal persons respond to *x*-rays by increase of metabolism, and that the leukemic successfully treated showed even more striking response, while, on the other hand, the leukemic unsuccessfully treated, and also two persons with gout had no noteworthy alterations in metabolism as a result of *x*-ray exposures, led to the conclusion that the changes in metabolism that occur as a result of exposure to *x*-rays are due to some response in the individual and not to any direct physical or other effect of the *x*-ray upon the tissues. The great rapidity of action of the *x*-ray upon metabolic processes, together with the other facts already mentioned, makes it seem highly probable that *x*-rays act in some way in increasing the ferment-like metabolic processes that are normal in the body; in other words, in stimulating autolysis. This becomes almost a definite fact when one considers that Neuberg has shown experimentally that radium increases autolysis *in vitro*.

The conditions in the case of chronic leukemia that was successfully treated with *x*-rays bore a striking resemblance to the conditions in acute leukemia, though they were not so extremely pronounced. The fact that autolytic processes can apparently be thus—*i. e.*, under the influence of the *x*-ray—changed from their normal state to one in which there is very unduly rapid tissue

[1] Reported, with Dr. Musser, in this volume (page 294).

destruction suggests strongly, I think, that the conditions in acute leukemia are actually due to some cause that similarly, though more markedly, excites an increase of autolytic tissue destruction.

Until the observations on the influence of the *x*-ray on metabolism in leukemia were made I was naturally inclined to believe that the conditions in acute leukæmia are a part of the malignancy of the disease. The effect of the *x*-ray on chronic leukemia, however, suggests strongly that the tissue destruction in acute leukemia may be not an essentially malignant process, but one that is of benign purpose. In chronic leukemia *x*-ray exposures produce, in cases successfully treated, a remarkably rapid tissue destruction that is evidently, from the clinical course of these cases, benign in its influence upon the organism. It seems wholly possible, therefore, that the destruction that occurs in acute leukemia is a response of the organism to the leukemic tissue hyperplasia, and is an attempt to control this and to destroy the leukemic tissue. It is not improbable, however, that if this is the case metabolic processes run amuck in the destruction of leukemic tissue, and carry the destruction so far that other tissues are involved to a dangerous degree; and, too, death is probably often hastened by the intoxication that results from the products of the rapid tissue destruction.

The fact that tissue destruction has not been found greatly increased in all cases of acute leukemia, but is so in most instances, tends rather to emphasize than to disprove this suggestion that the tissue destruction is an attempt at reaction on the part of the diseased individual, and that the purpose of the reaction is the destruction of diseased tissue. The fact that it is not constant indicates that the severity of the disease is not chiefly dependent upon the tissue destruction, and this latter point may readily be brought in harmony with the view that the tissue destruction is a part of the fight of the organism against the disease. Considering, again, the analogy between acute leukemia and chronic leukemia, when the latter is being treated by *x*-rays, the above suggestion concerning the purpose of the tissue destruction in acute leukemia becomes more emphatic when we remember that the tissue destruction in chronic leukemia that results from *x*-ray treatment

is limited almost entirely, perhaps entirely, to the lymphatic tissues and bone-marrow—that is, to the diseased tissues.

In conclusion, I would refer to the curiously low excretion of uric acid in the case of purpura hemorrhagica, which is of interest when contrasted with the large loss of nitrogen, and particularly with the extremely large amount of P_2O_5 lost. As will be noticed, on the day when hemorrhage was continuing the P_2O_5 excretion was above 6 gm., and on the next day it was still about 4 gm.; amounts that are very excessive at best, and that are particularly so in this instance, because there was no intake of P_2O_5. Indeed, a noteworthy amount more than this was probably excreted through his vomit. On the other hand the uric acid figures are about normal for a person who is temporarily taking no food; in fact, they are even rather low for such circumstances. The sources of the P_2O_5 are chiefly bone, nucleins and other parts of tissues, such as lecithin, that contain much phosphorus. That it came in this instance largely from the bones is, of course, very improbable at best, and is practically ruled out by the fact that the general nitrogen excretion was so great that it indicates marked destruction of nitrogenous tissue. It is, of course, possible that lecithin destruction, which, like bone destruction, would yield no uric acid, was responsible for the excessive P_2O_5 excretion, but it is very difficult to conceive of a process that would cause such an extensive destruction of lecithin and of nitrogenous tissues in general and leave the nucleins uninvolved. It seems far more probable that, as is usually the case, it came from nuclein, and that uric acid had been produced; but that, owing to some peculiarity in the disease or the individual, in this case the uric acid had been destroyed and was probably excreted as urea; while in most of the acute leukemia cases that have been studied the uric acid was not further changed, but was excreted as such. The observations of Magnus-Levy and others on hemorrhagic diseases did not include estimations of the uric acid and P_2O_5, so that I cannot state whether the conditions that I found are frequent in purpura and other hemorrhagic conditions or were merely peculiarities of this individual case. It would be of interest to determine whether this is a common feature in purpura hemorrhagica as contrasted with

other hemorrhagic conditions. If so, it would show that the metabolic disturbances of acute leukemia and purpura hemorrhagica, though they may closely resemble each other in a gross manner, may exhibit some striking differences in details. It would then be further evidence of the fact that has long been so evident, both clinically and pathologically, that hemorrhagic conditions of various sorts are very different in their natures, though the superficial resemblance provided by the hemorrhages leads, in a clinical discussion, to the inclusion of a number of those that are least understood under one general heading.

LITERATURE.

Magnus-Levy. Virchow's Archiv, Bd. clii.
Ebstein. Deutsch. Archiv f. klin. Med., Bd. xliv.
Wey. Ibid., Bd. lvii.
Wende. American Journal of the Medical Sciences, December, 1901.
Hawk and Gies. American Journal of Physiology, June, 1904.

A STUDY OF METABOLISM IN LEUKEMIA, UNDER THE INFLUENCE OF THE X-RAY.

WITH A CONSIDERATION OF THE MANNER OF ACTION OF THE X-RAY AND OF SOME PRECAUTIONS DESIRABLE IN ITS THERAPEUTIC USE.

By JOHN H. MUSSER, M.D., and DAVID L. EDSALL, M.D.,
of Philadelphia.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation.)

Recent observations and experiments have furnished most impressive testimony of the power of the *x*-rays for both good and evil, and the most remarkable of the favorable influences that have been observed in the past two years is that exerted upon leukemia. Indeed, in the extent of the tissue changes induced the effect in leukemia more than equals that seen in any other disease. It is true, to be sure, that, as is so commonly the case in cancer, the benign effect upon leukemia is only temporary, most of the cases in which apparent recovery occurred having relapsed, and none of them having as yet provided any evidence that relapse can be avoided. Nevertheless, numerous cases of leukemia have now been observed in which complete, or almost complete, temporary disappearance of symptoms was seen as a result of *x*-ray treatment, and an equal degree of success with other forms of treatment is rare to an extreme.

On the other hand, the evil effects of *x*-rays have attained recently a disquieting degree of prominence. For some time past occasional instances have been recognized in which, in leukemia and in other diseases, exposure to *x*-rays produced more or less severe and sometimes even dangerous febrile reaction,

chills, vomiting, prostration, and other pronounced general symptoms that had the appearance of being caused by an intoxication. We have also lately learned that occasionally serious lesions, such as nephritis, have followed the use of *x*-rays, and an astonishing and deplorable effect upon the reproductive function has been demonstrated by the work of Albers-Schönberg and others. Furthermore, Heineke, Warthin and others have described rapid and widespread changes in the tissues after the use of *x*-rays; the alterations in the lymph glands and bone-marrow found by Heineke in his extensive experiments being extremely startling and impressive.

It has, therefore, become plainly evident that in addition to the "burns" that have long given occasion for caution in the use of *x*-rays there are other unfortunate effects that may be more rapid in their appearance and that are at times much more grave. It is not surprising that an agent that is capable of producing profoundly benign effects should also have the power of doing great harm unless used with full knowledge of the manner in which its effects are brought about, and this has not been the case with *x*-rays. The indications for employing them and the dangers associated with their use have been determined chiefly by empirical means, while the nature of their action has remained a mystery.

Our investigations of the changes in metabolism that follow *x*-ray treatment of leukemia have demonstrated in a striking manner that the influence upon metabolic processes is extremely rapid and very profound, and our results emphasize most forcibly the possibilities in *x*-rays for the production of both good and bad results. They indicate also, we believe, with considerable clearness, the general way in which *x*-rays act.

The effect upon metabolism that we observed is probably unequalled by that known to be due to any other therapeutic agent. Radium is probably capable of equally marked effects, but it has not been studied in a similar way. Other therapeutic agents may, to be sure, have profound results when they are used in doses that largely exceed the therapeutic limit; but such results are definitely toxic, not therapeutic. With the *x*-ray, on the con-

trary, our observations appear to indicate clearly that tissue destruction is, in leukemia, evidence of favorable action, while when the *x*-ray fails to act this tissue break-down does not occur. This is a most striking fact and one that is quite the reverse of the usual conditions. Rapid break-down of body tissue is, of course, ordinarily extremely harmful, especially when protein tissue is being destroyed; in one of our leukemics, however, we observed the interesting phenomenon of rapid symptomatic improvement, occurring coincidently with tremendous acceleration of protein tissue destruction, while in the other leukemic, whose disease was progressing toward a fatality, the *x*-ray exerted extremely little influence upon metabolism, the destruction of tissue was scarcely at all excessive, and, as death approached, tissue break-down not only did not increase but appeared to grow progressively less. The changes that have been seen clinically and at autopsy in the condition of the spleen, the lymph glands and the blood, in cases of leukemia that have improved under this treatment, and particularly the remarkable experimental work of Heineke, appear to show that the tissue destruction produced by the *x*-ray is limited largely to the lymphatic tissues and the bone-marrow; Heineke, indeed, could find no changes in other tissues. Hence, the fact that symptomatic improvement occurs in leukemia while tissues are undergoing rapid destruction seems to be the result of the limitation of this tissue disintegration, chiefly, or possibly entirely, to the diseased parts.

Rather than lessening its importance, this apparent limitation of the effects to certain tissues adds to the interest of the subject in its relation to general metabolism.

Our studies of the behavior of metabolism in leukemia while *x*-ray treatment was being used were, as we have already indicated, carried out in two cases. We wish particularly to emphasize the contrast between these two cases, for the opportunity to compare the conditions during successful treatment with those during unsuccessful treatment led to what is, perhaps, the most suggestive result of the study. One case had previously been subjected to this treatment with success, and nearly all symptoms

had then disappeared; but they returned, and when our observations on metabolism were made the symptoms were growing worse continuously, in spite of the use of *x*-rays, and the patient soon died. In the other case, on the contrary, severe symptoms were present when *x*-ray treatment was instituted, and the patient was growing worse at that time; but the use of *x*-rays resulted in immediate and very rapid improvement and the patient left the hospital a few weeks later, showing only slight evidences of leukemia.

The influence of *x*-rays upon metabolism was studied also in two cases of severe gout (by Dr. Edsall and Dr. Fife), and in another case (Dr. Edsall) in which the conditions of metabolism were practically normal. The details of these cases will be published elsewhere, but the results will be referred to in this paper in so far as they bear upon the conclusion to be reached concerning the way in which the *x*-ray acts.

Both leukemics were private patients of Dr. Musser. Both were told that *x*-ray treatment of leukemia is still somewhat of an experiment, and that there is an element of danger in it, but both wished the treatment to be tried. It was impossible to subject them to rigid limitation of the diet for a long time. Both had poor appetites, particularly the first patient, and they soon rebelled against the monotonous diet; consequently the period of study was brief, and some minor details (such, for example, as the duration of the effect of the *x*-ray) that could be determined only by more prolonged study were necessarily left unsettled. The main points sought for were, however, made sufficiently clear by the results that were secured. The figures obtained in both cases in the study of metabolism will, for the sake of contrast, be put together, following the clinical synopsis of the two cases.

Only the main clinical details will be given.

Case I.—The fatal case. The patient, E. C. H., a man aged forty-four years, a plumber, was first admitted September 15, 1904, to the private wards of the University Hospital. He had no family or personal history that was of any noteworthy consequence until March, 1904, when he began gradually to lose strength. The weakness had increased from this time, but he had

noticed no other symptoms, except mental irritability and occasional attacks of diarrhea. At the time of admission he showed the conditions usual in a marked splenomyelogenous leukemia. The spleen then extended from the seventh rib in the anterior axillary line to three inches below the level of the umbilicus, and anteriorly nearly to the median line, its greatest length being twelve and one-half inches, its greatest breadth thirteen inches. The liver was not enlarged; the inguinal and axillary glands were palpable, but not of large size. The blood examination showed hemoglobin, 38 per cent.; red blood cells, 4,280,000; white blood cells, 407,500. A differential count made on the 21st showed:

Myelocytes	49.2 per cent.
Polymorphonuclears	27.1 "
Transitionals	21.6 "
Eosinophiles	1.0 "
Lymphocytes	0.2 "

There were also 0.8 per cent. of nucleated reds. The patient was at once put upon x-ray treatment and very rapidly improved, the behavior of his leukocytes being shown by the accompanying chart that was made by the resident physician, Dr. Thomas Kelly. The continuous line indicates the counts before the x-ray treatments; the broken line the counts taken directly after the x-ray treatments.

At the time of discharge, on October 13th, the leukocyte count was 138,000; the spleen had decreased greatly in size and the patient's general condition was very much improved. The leukocytes subsequently fell to below 35,000, and the spleen became about normal in size. He left because of the demands of his business, but had x-ray treatments at first daily; afterward once or twice a week until February, 1905. He then stopped coming for treatment. He was readmitted on March 12, 1905, having rapidly grown much worse, and having recently had pain and soreness in the muscles, with fever and considerable weakness, and with renewed enlargement of the spleen. Upon examination his spleen was found to reach the level of the umbilicus and the leukocyte count was 180,400.

The differential count (Dr. A. O. J. Kelly) showed:

Basophiles	4.0 per cent.
Lymphocytes	4.0 "
Polymorphonuclears	18.0 "
Eosinophilic myelocytes	2.5 "
Neutrophilic myelocytes	71.5 "

Several nucleated reds were seen. The man had slight fever, which continued afterward, running as high as 101°. He grew rapidly worse, and on the 21st, the day that the observation of metabolism was started, his leukocyte count was 304,000. Because of his bad condition the preliminary observa-

tion of metabolism was continued but two days, and on the 23d *x*-ray treatment was started. For several days after this he seemed to feel better, though there was no improvement in the leukocytes; on the contrary, they grew continuously more numerous, the count being 453,600 on the 26th and 496,000 on the 29th. He also developed fresh hemorrhages into the retina. Suddenly, on the 31st, he went into temporary collapse. The following day he was very weak, and early the next morning he again went into collapse and died. A postmortem could not be secured.

Case II.—The successful case. The patient, Mrs. L., aged forty-two years, was admitted to the private wards of the University Hospital on March 20, 1905. Her history previous to October, 1903, was without interest. At that time she became easily fatigued, lost flesh, and her color rapidly changed and became "greenish." She also noted enlargement in the splenic region. After general treatment she improved very greatly, and by the spring of 1904 had, she believed, regained her normal health. This continued until October, 1904, when she had a slight operation for a cyst of the eyelid, and hemorrhage continued for nine hours from the small incision. She lost a great deal of blood and was much shocked afterward, and her spleen almost at once became enlarged, while her general condition grew gradually worse up to the time that she was admitted. When seen by Dr. Musser she presented marked features of leukemia, the spleen extending from the seventh interspace in the anterior axillary line to within an inch of Poupart's ligament, while anteriorly it reached beyond the median line. The liver was not enlarged; there was no marked glandular enlargement. The blood count showed 68 per cent. hemoglobin, 3,410,000 red blood cells, 245,000 white blood cells.

The differential count (Dr. A. O. J. Kelly) showed:

Neutrophilic myelocytes	45.0 per cent.
Basophilic myelocytes	16.0 "
Eosinophilic myelocytes	3.0 "
Polymorphonuclears	26.0 "
Lymphocytes	9.0 "

The patient was weak and very pallid and appeared emaciated. She felt worse during the next few days, and on the 23d, when the metabolism experiment was started, the leukocyte count was 272,000; on the 26th, when *x*-ray treatment was begun, it was 304,400. Directly after this continuous improvement began and the spleen decreased rapidly in size, so that on April 20th, when she was discharged, the lower border was but slightly below the umbilicus, and the anterior border was fully two inches within the median line.

The leukocyte counts had been as follows: March 27th, 262,400; 28th, 252,400; 29th, 246,400; 30th, 214,400; 31st, 191,200; April 1st, 149,600; 4th,

TABLE 1. CASE I. PRELIMINARY PERIOD.

Date.	Urine.				Feces.		Total loss in excretions.		Intake in food.		Balance.	
	Nitrogen.	Uric acid.	Purin bases	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.
March 22	6.6662	lost	0.0863	0.680	1.152	0.937	7.8182	1.6170	8.5754	4.4288	+ 0.7572	+ 2.8118
" 23	9.9552	1.9625	0.0618	0.7296	1.152	0.937	11.1072	1.6666	10.3262	4.1127	— 0.7810	+ 2.4461
Total	16.6214	.....	0.1481	1.4096	2.304	1.874	18.9254	3.2836	18.9016	8.5415	— 0.0238	+ 5.2579
Average	8.3107	1.9625	0.0740	0.7048	1.152	0.937	9.4627	1.6418	9.4508	4.2707	— 0.0119	+ 2.6289
					X-RAY PERIOD.							
March 24	7.6608	1.7437	0.0430	0.8640	1.229	0.993	8.8898	1.8620	8.5693	3.7003	— 0 3205	+ 1.8383
" 25	7.4480	1.6425	0.0654	1.1712	1.229	0.998	8.6770	2.1692	8.2309	3.8854	— 0.4461	+ 1.7162
" 26	7.9520	1.8490	0.0678	1.2800	1.229	0.998	9.1810	2.2780	9.1542	4.0788	— 0.0268	+ 1.8008
Total	23.0608	5.2352	0.1762	3 3152	3.687	2 994	26.7478	6.3092	25.9544	11.6645	— 0.7934	+ 5.3553
Average	7.6869	1.7430	0.0587	1.1050	1.229	0.998	8.9159	2.1030	8.6514	3.8881	— 0.3967	+ 1.7851

Average calories in daily diet: Preliminary period, 1230. *X*-ray period, 1230.

TABLE 2. CASE I. IN PERIOD FOLLOWING DETERMINATION OF METABOLIC BALANCE, X-RAYS STILL BEING USED.

Date.	Nitrogen.	Uric acid.	P_2O_5.
March 27	6.1340	0.5422	1.2480
" 28	5.1744	0.5445	0.8442
" 29	3.3260	1 1236	0.4800
" 30	3.7796	1.4033	0.6144
" 31	4 9440	0.9035	0.6912

Died April 2d.

Table 3. Case II. Preliminary Period.

Date.	Urine.				Feces.		Total loss in excretions.		Intake in food.		Balance.	
	Nitrogen.	Uric acid.	Purin bases.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.	Nitrogen.	P_2O_5.
March 24	8.8032	0.8925	0.0585	0.9744	1.684	1.737	10.4872	2.7114	12 2022	5.5623	+ 1.7130	+ 2.8509
" 25	8.1600	1.1390	0.0333	1.3008	1.684	1.737	9.8440	3 0378	12.5060	5.8678	+ 2.6620	+ 2.8300
" 26	9.2736	1.1320	0.0406	1.7220	1.684	1.737	10.9576	3.4590	12.8227	5.7196	+ 1.8651	+ 2.2600
Total	26.2368	3.1635	0.1324	3.9972	5.052	5.211	31.2888	9.2082	37.5309	17.1497	+ 6.2401	+ 7 9409
Average	8.7456	1.0545	0.0441	1.3324	1.684	1.737	10.4296	3.0694	12.5103	5.7165	+ 2.0800	+ 2.6469
					X-ray Period.							
March 28	14.3920	1.6750	lost	2.944	1.660	1.624	16.0520	4.568	11 5686	5.2803	— 4.4834	+ 0.7123
" 29	15.3300	1.5800	0.1403	3.246	1.660	1.624	16.9900	4.870	11.2949	5.4140	— 5.6951	+ 0.5440
" 30	14.6588	1.6180	0.1623	3.048	1.660	1.624	16.3188	4.672	11.4077	5.6659	— 4.9111	+ 0 9939
Total	44 3808	4.8730	0.3026	9.238	4.980	4.872	49.3608	14.110	34.2712	16.3602	— 15.0896	+ 2.2502
Average	14.7936	1.6243	0.1513	3 0793	1.660	1.624	16.4536	4.703	11.4237	5.4534	— 5.0298	+ 0.7500

Average calories in diet: Preliminary period, 1750. *X*-ray period, 1410.

Table 4. Case II. In Period following Determination of Metabolic Balance, X-rays still being Used.

Date.	Nitrogen.	Uric acid.	P_2O_5.
March 31	13.4064	2.0040	3.1392
April 1	14.0616	2.4274	3.0400
" 2	15.3216	1.9672	2.5920
" 3	13.9216	2.2811	2.9040
" 18	10.3320	0.8329	1.9488
" 19	12.4236	1.2219	2.9538

96,000; 5th, 80,080; 7th, 40,080; 9th, 32,800; 11th, 30,400; 13th, 24,720; 15th, 28,440; 17th, 17,440; 18th, 15,200; 20th, 15,360. She returned for blood counts and x-ray treatment until May 8th. During this time the counts were: April 26th, 12,480; 30th, 6480; May 8th, 9040.

For the study of metabolism both patients were put upon a diet of milk, bread, butter, eggs, sugar, rice, steak, baked potato. The amount taken each day was kept as nearly the same as possible, and the quantity actually taken was accurately weighed each day; it was not possible with either patient to make the daily intake absolutely uniform, but the variations were slight and not important.

The amount of nitrogen and P_2O_5 in the food in each case was calculated partly from a large series of analyses that we had previously made of the same foods as they are used in the University Hospital, partly from the figures of König and Blythe, chiefly from our own figures. The nitrogen, P_2O_5, uric acid (Folin-Schaeffer method) and purin bases (Salkowski method) of the urine were estimated daily. The feces for each period were collected as a whole, dried, ground and the nitrogen and P_2O_5 contained in them estimated in a number of different portions. The total amount in the feces was determined from the average of these estimations. In both cases the diet was given for three days before the metabolism experiment was begun. In both instances there was then a preliminary control period of observation of metabolism, which was made very short in each instance, because both patients were so ill that it seemed unjust to delay the use of x-rays for a longer time; this period was two days in length in the first case, three days in the second. There was then a period of observation, three days long in both cases, during the use of x-rays. After this it was necessary to relinquish the rigid diet, since both patients refused to take it longer. Consequently the intake could no longer be accurately determined, but for some time afterward the nitrogen, P_2O_5 and uric acid of the urine were determined in each case and the figures obtained, which provide some interesting observations, will be given in separate tables following those that exhibit the metabolic balance.

The condition of general nitrogen metabolism before *x*-ray treatment was begun is of interest in itself. The studies of von Noorden, Magnus-Levy and A. E. Taylor have shown that in the ordinary course of chronic leukemia nitrogen metabolism may show a balance, a slight loss or a retention. It is not surprising that this is the case, for the clinical course of the disease would lead one to anticipate it. It is, however, an interesting contrast to the conditions in acute leukemia, for most cases of the latter disease whose metabolism has been studied have shown a loss so large as to be but rarely equalled in other diseases. In a case recently studied by one of us the nitrogen loss through the urine was over twenty-two grams, and the whole loss was, indeed, much more than this if the loss by hemorrhage be included.

The most interesting point in this connection, however, in regard to the cases now under discussion is the fact that both our patients during the preliminary studies of metabolism were very ill, and were rapidly growing worse, the first case in particular exhibiting fever, increasing prostration, and other appearances of a toxemia that was hastening toward a fatal issue, and yet there was even in this case no evidence of excessive general tissue destruction, and in the second case there was marked retention. The same point has been observed by others. Apparently, therefore, the toxemia that occurs in the most severe stages of chronic leukemia does not necessarily produce tissue loss. One would think at once of the possibility that in these cases a generous food allowance had sufficed to conceal the evidences of tissue loss, for it has been shown that abundant feeding in the course of toxemias may at times transform the loss that usually occurs to a balance between the intake and outgo, or may even produce some retention. This, however, was certainly not the explanation in these cases, for, as can be seen from the figures, the amount of protein consumed was less than the normal, and the total value of the food in calories was very low. Hence, it appears that in these cases there was severe toxemia; and not only was there no evidence of any noteworthy increase in destructive processes, there was in one case actual decided retention that was probably due to the disease, an interesting contrast with most

infectious toxemias, with cancer and with many nutritional diseases, such as exophthalmic goitre, Addison's disease, advanced diabetes and gout (at the time of acute attacks). In the latter conditions and in many other endogenous and exogenous intoxications, more or less marked nitrogen loss occurs, as an almost constant expression of the intoxication. It is uncommon, indeed, to find a marked toxemia in which tissue loss does not occur; and hence the presence of a grave toxemia associated with retention is the more interesting. Most of the amount that was retained was probably used in making leukemic tissue. It of course occurs to one at once that the retention was due merely to poor excretion, but this possibility does not seem of much consequence when one considers that our second patient promptly almost doubled her excretion when *x*-rays were used, and that the patient with acute leukemia, whose case was mentioned above, excreted enormous quantities of solids, in spite of the fact that he had extremely severe kidney lesions. The patients at present under discussion had no evidence of nephritis, and there is no reason why they should have had marked incompetence of the excretory organs.

Another point seems to be clearly shown by the figures. The products of disintegration of leukemic tissue do not appear to have any essential relation to the toxic symptoms that may occur in chronic leukemia. Both our cases, while retaining nitrogen, were growing worse; one, immediately upon the beginning of very rapid tissue destruction, began to grow better; the other, having no increase of tissue destruction, continued to grow worse. Other cases that have improved largely upon the use of *x*-rays have almost certainly had tissue destruction similar to that which occurred in our successful case. The tissue that is destroyed in these cases is chiefly, if not entirely, the leukemic tissue. Therefore, we must, in this disease at least, restrict the idea that is so frequently expressed in connection with many nutritional disorders, that the toxic symptoms are chiefly due to the products of disintegration of tissue.

There are at times, however, symptoms of marked toxemia in chronic leukemia, especially in the later stages, and such symp-

toms were present in these cases, particularly in the first. It seems probable that these symptoms are produced either by products elaborated by leukemic tissue in the ordinary course of metabolism, these products differing from those furnished by normal tissues of the same organs in being more toxic; or the symptoms may be due to poisonous substances elaborated in the course of the synthetic processes that go on during the actual building up of the leukemic tissue. The former seems in many ways the readiest explanation of the symptoms, but the latter thought cannot be wholly dismissed, particularly when we consider that active increase in the splenic enlargement and in the number of leukocytes, is often coincident with signs of increasing toxemia; while, on the other hand, if the disease is not progressing rapidly, there may be little or no evidence of intoxication, in spite of the presence, perhaps, of very extensive leukemic deposits, and in spite, therefore, of the fact that these leukemic deposits are playing a large role in the individual's metabolism. The first-mentioned conditions occurred in our cases before *x*-ray treatment, and both patients were then constructing tissue. When in our second case tissue destruction became largely in excess of construction the toxic symptoms disappeared; but in the other case there was no increase of tissue destruction, construction apparently continued, and probably increased, and the toxic symptoms grew worse.

The condition of phosphorus metabolism is of interest because there was so marked a retention. A similar condition has been previously observed by Moraczewski, while some other authors have found a balance or a phosphorus loss. Taylor considers a phosphorus retention very surprising in the light of our knowledge of leukemia. It does not appear to us to be so remarkable. Leukemics whose disease is progressing constantly construct tissues that are rich in phosphorus, and naturally if their tissue construction is largely exceeding the loss—and the condition of nitrogen metabolism shows that this was clearly the case in the second of our patients—there will be a retention of phosphorus in the construction of phosphorus-containing tissue; and since leukemic tissues are of the class that contain a large amount of

phosphorus, the phosphorus retention is likely to be relatively large.

There are, to be sure, large deposits of leukemic tissue in persons with leukemia, and since this tissue contains large amounts of nucleins the excretion of products of disintegration of nucleins (uric acid, purin bases, phosphates) is likely to be high; and as a matter of fact these substances are, as is well known, usually found in large amounts in the urine of leukemics. This large excretion does not mean, however, that retention of the constituents of nuclein-containing tissue cannot occur in these cases. It is apparently merely a question as to whether the construction or the destruction of these tissues is more active at the time of observation.

To turn to the effects of the *x*-ray, reference to the figures in the second case—the one that rapidly improved—shows a transformation upon the use of this treatment that was most remarkable in its extent, and particularly in the rapidity with which it occurred. The changes in the average daily excretion in the urine were as follows: The nitrogen rose from 8.7456 gm. to 14.7933 gm.; the uric acid from 1.0545 gm. to 1.6243 gm.; the purin bases from 0.0441 gm. to 0.1513 gm.; the phosphates from 1.3323 gm. to 3.0793 gm. The average increase was therefore as follows: nitrogen, 6.0477 gm.; uric acid, 0.5698 gm.; purin bases, 0.1072 gm.; phosphates, 1.7469 gm. The increase put in the form of percentage of the amount previously excreted was, in round numbers: nitrogen about 70 per cent., uric acid about 60 per cent., purin bases about 260 per cent., phosphates about 200 per cent. The diet remained practically the same during this time; the monotonous food had, to be sure, become somewhat repulsive to the patient, and she refused to take quite as much as before; but consideration of this fact makes the result more striking, not less so, for normally reduction of the intake within reasonable limits is, of course, almost at once followed by decrease of the outgo, while in this instance there was greatly increased excretion, in spite of somewhat reduced intake. The change in the diet was, however, of little consequence, and the amount of food remained sufficient to have maintained a distinct

nitrogen retention had the excretion remained the same; but, as a matter of fact, the excretion became suddenly so largely increased that a previous decided nitrogen retention immediately became a very marked nitrogen loss. The break-down of nitrogenous tissue produced by the *x*-ray was at least equivalent to the difference in the excretion in the urine before and during *x*-ray treatment, for beyond the use of *x*-rays in the second period there was no factor that was changed to any appreciable degree. As was stated, this difference in the nitrogen excretion was 6.0477 gm.; that is, about 70 per cent. of the previous excretion. Tissue break-down was, however, almost certainly increased much more than 70 per cent., because much of the nitrogen excreted in the preliminary period was derived from the food, while all the increase in the *x*-ray period came from the tissues, since there was no increase of the food in this period. The last statement is true also of the uric acid, purin bases and phosphates; the uric acid increase was about 60 per cent., that of the purin bases about 260 per cent., of the phosphates about 200 per cent.; but even these figures do not indicate the whole of the increased break-down of tissues of the kind that yield these substances, for a large part of the excretion in the preliminary period was unquestionably derived from the food, particularly a large part of the phosphates. It may safely be said that the tissue break-down in general was increased more than 100 per cent. in the three days immediately following the institution of *x*-ray treatment, and most of this increase occurred immediately. This statement, indeed, seems very conservative when one observes not only the figures for the urine, but more especially those for the balance.

After this time the intake of nitrogen and phosphorus could not be accurately determined; the subsequent figures are, therefore, less valuable, though they show clearly a marked further increase in uric acid excretion. Nevertheless, as far as it was possible to calculate them in the varied diet that the patient got after this period the nitrogen and phosphorus in the food were found to be for some time, until the patient's appetite improved, decidedly below what they were when she was on rigid diet.

Hence, there is little doubt that she actually had, for some days at least, after we ceased determining the balance, an even more marked tissue destruction than she had during the time that the balance was known. However, the change that can be seen in the three days during which the balance was determined is sufficiently amazing.

It is a somewhat surprising fact that although the phosphorus excretion showed an even more remarkable increase than did the excretion of nitrogen and uric acid the phosphorus balance still showed that there was a retention even after *x*-ray treatment was begun. It is not possible to explain this definitely. The suggestions that most readily occur to one are that the patient, though breaking down nucleoprotein, was building up other tissues that contain substances, such as lecithin, that are rich in phosphorus; or that the products of the phosphorus-containing portion of the destroyed nucleoprotein were excreted slowly as compared with the nitrogen. The latter seems more probable. Nucleoprotein, in the course of ordinary digestion experiments, quickly breaks up (Umber) into albumin and nucleic acid. Albumin very rapidly undergoes further disintegration, while this apparently occurs more deliberately with nucleic acid; therefore, most of the nitrogen from nucleoprotein would appear quickly and purin bodies and phosphates more slowly. Evidence that this was probably the course of events in this case is seen in the fact that the uric acid excretion reached its height only after several days, while the nitrogen excretion rose at once to about the level that it maintained subsequently. Furthermore, after the patient was allowed her choice of food the intake was, as was stated, reduced much below the previous point, and at this period a rough calculation of the intake indicated a phosphorus loss. The phosphorus excretion represents the effects of the *x*-ray much more definitely than does the phosphorus balance in this short period.

As we have already stated, results as striking as those we have mentioned are, so far as we know, not produced by any other therapeutic agent unless the dose used is such as to give rise to acute toxic effects. In this leukemic not only was the effect of

x-rays not damaging; it was profoundly benign. There was a rapid tissue loss such as is seen in severe intoxications caused by infections and by many direct chemical poisons, and occasionally in nutritional diseases; but, instead of increasing the evidences of intoxication that were already present in this case, the process that produced the tissue destruction caused the appearances of intoxication to vanish rapidly and the patient began quickly to regain symptomatic health. This condition of affairs is extremely striking in its contrast with common experience in other circumstances.

The results in the first case offer a remarkable comparison. They will be discussed somewhat further in considering the manner in which the *x*-ray acts, for they are of importance chiefly in that connection. At present it is of interest merely to refer to the fact that the figures show that *x*-ray treatment had no marked influence upon this man's metabolism. There was, apparently, a slight effort at increased metabolism, for the excretion of phosphates showed a noteworthy rise, and there was a slight loss of nitrogen, as shown by the nitrogen balance; but the phosphate excretion soon fell back in the period following the formal metabolism experiment, and, except for the fact that the uric acid excretion remained somewhat excessive, as it usually is in leukemia, the excretion was persistently low; most strikingly low, indeed, for a man who was suffering from an intoxication so severe that it soon caused his death. This low excretion was, of course, largely due to a small intake of food, but this does not influence the fact that there was, at most, no noteworthy tissue loss.

As we have before remarked, our results in the successful case demonstrate in a very impressive way the profound power of the *x*-ray in influencing tissue processes. They show clearly that a very important effect, possibly the only important one, is an almost immediate increase in tissue destructive processes. This occurs not only in leukemics, but in normal persons as well. Baermann and Linser have found an immediate, though less striking, increase in nitrogen metabolism in normal persons. They did not study the excretion of other substances, but Heile

made some fragmentary and brief observations on the excretion of purin bases and uric acid in persons with various pathological conditions, and his results are in consonance with our own observations. Other studies made by one of us (Edsall, partly with Dr. Fife) in gout and in other conditions also show that the increase of metabolism is not confined to leukemics, but they likewise indicate that it does not occur in all diseases.

There are certain conclusions that are of direct practical interest to be derived from the facts that have been discussed. That acceleration of metabolism may be very useful in many obscure disorders of nutrition, in which there is apparently slow or imperfect disintegration of food or tissues, is a possibility that will be granted at once, and the effect of *x*-rays may properly be tried with caution in a considerable number of nutritional disorders, both because favorable clinical effects may perhaps be seen, and because a means of stimulating metabolism is something that has been much desired for purposes of investigation, and it may make it possible for the student of nutritional diseases to secure extremely useful knowledge concerning the nature and treatment of many of these diseases. There are already apparent, however, in previous clinical experience with *x*-rays, and in our own studies of metabolism, a number of facts which make it evident that the influence of the *x*-ray upon metabolism is likely to be limited in its clinical usefulness, and there are also facts which show that grave damage may result from the use of this treatment in some conditions, unless much caution is exercised. Some of these points relating to other disorders than leukemia are not germane to the present discussion, and will therefore be referred to elsewhere; other points, however, and particularly those that relate to the dangers in the use of this agent, require some mention, since the emphasis that our study lays upon them and the new facts that it brings out are of direct importance to the clinician. Our results appear to demonstrate, too, the manner in which some of these dangerous results are produced, and indicate the necessity for special caution in the use of *x*-rays when certain diseases are present.

It is not necessary to insist that any method of treatment

that may cause a patient to double his tissue break-down requires care in its use, if dangerous results are to be avoided. It is true that the tissue destruction produced in leukemics is probably rarely, if ever, equalled in normal persons, and only infrequently in persons with other diseases. It is likewise true that vast numbers of persons have been exposed to *x*-rays with such usual absence of apparent general effects that there has until recently been little fear of any bad results, excepting purely local ones. But it should, at the same time, be kept clearly in mind that an effect so profound and unfortunate as is sterility may apparently occur readily, and yet the evidence that it has occurred appears only when deliberate investigations are undertaken to demonstrate that it has resulted. This makes one at once consider the possibility that other similarly unfortunate effects that are at present obscure may result. Certainly one can scarcely doubt that the sudden necessity for completing the disintegration of as large an amount of tissue as our second patient destroyed daily, and the excretion of the end products of these tissues may prove to be a severe tax upon many of the organs concerned in metabolism and upon the excretory organs, especially the kidneys. It is not surprising to learn that severe kidney lesions have been produced in leukemia, and even in other disorders. If Heineke's observations are correct these kidney lesions are not a result of the direct action of *x*-rays; and if this is the case our observations seem to demonstrate the reason for their occurrence. The increased excretion that our second patient accomplished shows what is demanded of a leukemic who is successfully responding to *x*-ray treatment; and while this demand may safely be made temporarily of one whose organs are sound, there may be dangerous consequences with any patient, whatever his disease, if the labors of his excretory organs are suddenly doubled, when they are, perhaps, already taxed nearly to their utmost capacity.

The remarkable tissue destruction that we observed furnishes also a probable explanation of the curious toxic symptoms that have occasionally been noted after the use of *x*-rays. A sudden flooding of the organism with products of tissue break-down

may readily be sufficient in itself to cause intoxication, and it may also readily overtax the catabolic and excretory functions of various organs and render them unequal to even their previous tasks. The organism has such elasticity of function that harm probably results but rarely in persons whose powers are not already crippled, and evident harm has certainly not often been observed in anyone. But the potentiality for harm certainly exists, and, while there is comparatively little knowledge as yet of such harmful effects, it must be remembered that the study of the dangerous general effects of *x*-rays has been arousing interest for but a short time, and nevertheless it has already proved surprisingly fruitful. Comparatively few conditions, too, have been studied in this connection, and broader investigation may develop further harmful effects beyond those now known.

We would not be thought to desire to condemn offhand the use of *x*-rays. We believe, on the contrary, that the demonstration that *x*-rays may profoundly influence metabolism indicates the possibility of their good effects quite as forcibly as it shows the possibilities of bad results from them; and clinical experience has already clearly shown their great value in some conditions. We would, however, insist that the extent and importance of their effects upon tissue processes is just beginning to be appreciated, and that the power to produce such effects carries with it the power to produce great harm at times unless the general manner of action is appreciated and the danger is carefully avoided.

The most impressive illustration of this fact that we have seen was furnished by two cases of pernicious anemia that were treated by *x*-rays at the Episcopal Hospital. The first patient, a woman, was admitted to the service of Dr. D. J. Milton Miller, who has previously described her case in a discussion before the section on medicine of the College of Physicians of Philadelphia. Since this patient did not respond to the ordinary treatment she was given one exposure to *x*-rays. The result was a violent chill, high fever, prostration and rapid increase in the anemia. Two weeks later, April 1, 1904, when in the change of services she came under the care of one of us (Edsall), her red

blood cells had fallen from 928,000 to 600,000. She was delirious and profoundly prostrated and death ensued a few days later.

The second case, a man, was admitted to the service of Dr. Elliston J. Morris in May, 1904. He grew progressively worse under the use of arsenic and other measures, the red cells falling in about a month from 1,212,000 to below 750,000. *x*-rays were then tried as a final resort. He at once began to improve; continued to do so, and left the hospital six weeks later in excellent general condition and with 3,600,000 red cells. In May, 1905, he was admitted to the service of Dr. Edsall with a relapse, his red cells being then 1,544,000. Again *x*-rays were used, and again he gained, his red cells increasing in a week to 2,100,000. There was no further improvement after this time, however, under *x*-rays or other treatment, and when last seen at the end of July, 1905, his general condition remained much the same, while his red cells had slightly decreased. Why one patient was apparently so gravely damaged while the other improved so strikingly (in his first attack) could not be determined. The exposures were about the same in both instances. The one case shows, however, the necessity for caution in the use of an agent that may be very dangerous. The other case demonstrates the desirability of determining more clearly than has been done the conditions that permit of the safe employment of a treatment that may apparently do much good in some instances when other measures have failed; though one must, of course, hold in mind the well-known fact that cases of pernicious anemia are often extremely fitful in their progress toward improvement or relapse, and this may perhaps explain the improvement in the man.

One suggestion, however, that may have some value as a guide in other cases may be made as a result of these observations. The man who improved showed at the time *x*-ray treatment was begun no symptoms beyond characteristic and severe blood changes, and the weakness and other general symptoms that always accompany grave anemia. He showed no evidence that he was suffering at that time from an intoxication, beyond the

mere fact that he had pernicious anemia, which disease is commonly believed, though not demonstrated, to be an intoxication. On the other hand, the woman, who died, had already more suggestive clinical appearances of intoxication before *x*-rays were used, for while the condition of her blood was at that time much better than that of the man when his *x*-ray treatment was begun, her general condition was much worse. Her temperature also fluctuated somewhat, and she had gastric symptoms, which, while common in pernicious anemia and perhaps often dependent upon atrophic gastritis, are not improbably frequently one expression of a toxemia in this disease, as they are in many other diseases. While it is not at all clear that this was the cause of the difference in the results in the two cases, it is quite possible that the woman was already struggling with a severe toxemia, and the added demands that were due to the tissue destruction that the *x*-ray excited overwhelmed her; whereas the man's metabolic and excretory functions were doing less severe duty and were capable of completing the extra labor that was thrown upon them. This hypothetic explanation is not offered because it is in itself of any special value, but because it seems to give reasonable occasion for caution in the use of *x*-rays when the clinical appearances of a toxemia are present.

We are convinced that there has been too great freedom in the use of *x*-rays. Not that the sphere of their usefulness is likely to be narrowed; it will, on the contrary, probably be widened, but it should be widened by tentative trial of the effects in individual cases, and with careful watching for the evil results that are known to occur and for others that are not yet recognized. So far as has been shown by studies of metabolism, by changes in morphology or by clinical observation, bad general results are not likely to occur if the exposure is brief and the dose not severe; and the point of chief importance in avoiding danger seems at present to be the use of a very small dose and a brief exposure until, in individual cases, it is determined that harm does not result, the dose being subsequently increased slowly if desired. It is of equal importance, however, to watch alertly at the same time for evidences in the urine or elsewhere of resulting damage.

It has not been a sufficiently general custom to follow such a plan, the chief point customarily observed having been the avoidance of burns. The determination of the dose and the exposure should not be left wholly to the *x*-ray expert, but should be largely reached through the attending physician's general knowledge of the individual patient. The evil custom that is so prevalent of merely sending a patient to an *x*-ray expert with a statement of the condition to be treated should cease, and both physician and *x*-ray expert should regularly consider the possible general effect, as well as the local, in the individual who is to be cared for. It seems not improbable that studies of the effect of *x*-rays upon excretion in various diseases, and particularly studies in individual cases that arouse apprehension, will prove a help in determining which diseases and which individuals may be treated with considerable impunity, which require very careful and deliberate progress, and which should not be treated at all by this agent. Certainly, however, there can be no doubt at present that the existence of nephritis should make one very cautious in using *x*-rays, and a good deal of care should also be exercised when there is already any form of toxemia.

There is one point that has been dwelt upon chiefly by morphologists and has caused a good deal of apprehension that seems to us to be less an indication of danger than it is now generally thought to be. This is the widespread occurrence of necrosis in the lymphatic tissues in leukemics and others who have been treated with *x*-rays. This is often considered evidence of the dangerous effects of *x*-rays, but its occurrence in leukemia and in other diseases involving the lymphatic tissues appears to be actually evidence that the *x*-rays are accomplishing the purpose for which they are being used. Such changes show the necessity for caution, but instead of growing frightened about them one should probably consider them evidence of improvement in some diseases. The same effect is observed in the lymphatic tissues of normal persons, however, and in such persons, as well as in many diseases, it cannot be useful. How far extensive destruction of lymphatic tissue is a source of immediate danger to the normal organism is as yet unknown, but it is a striking fact that Heineke,

in his animal experiments, saw no noteworthy symptoms that were evidently due to the destruction of lymphatic tissue, while later, when extensive bone-marrow changes occurred as a result of prolonged exposures, he did see very severe symptoms that resulted in death.

In concluding we may refer to the manner in which *x*-rays act. It is not possible from clinical observation, or from studies of the morphologic changes alone, to determine whether the effects are due to some physical or other direct influence of the *x*-ray or to some peculiar response of the individual to stimulation of functions that lie within himself. It is, of course, known that some cases improve while other cases of the same diseases do not improve; and also that the individual leukemic, for example, may at one time grow vastly better and later show no effect; but such observations do not demonstrate the existence of reaction or lack of reaction of the individual, for they may be explained on the supposition that in any of these instances the *x*-ray is exerting a direct influence that is peculiar to itself, but the disease, in unfavorable cases, is progressing so persistently and rapidly that it keeps ahead, so to speak, of the effect of the *x*-ray.

Our studies, however, have shown clearly, we think, that the influence is not direct, but is due to the power of the individual to respond to stimulation. This is of much interest from a practical as well as a theoretical standpoint.

To make this point clear we would again refer to the fact that the one leukemic who improved showed a striking effect upon metabolism during this improvement; while in the other case lack of improvement was associated not merely with evidence that the effect of the *x*-ray did not keep pace with the disease, but actually with evidence that there was practically no influence upon metabolism. Furthermore, Baermann and Linser, as was noted, have shown that the nitrogen metabolism of normal persons is decidedly increased by *x*-rays, and we have demonstrated the same fact, as well as a large increase of uric acid excretion, in a person whose metabolism was practically normal. In addition to this we would mention with some emphasis the cases of gout previously referred to, in which nitrogen and phosphorus metabolism and uric acid

and purin base excretion were determined. It is an extremely striking fact that neither of these cases showed any distinct effect of *x*-rays upon metabolism. It is well known that patients with gout tend, as a rule, to have a very low excretion in the interval, while the excretion shows an apparently toxic increase with the attack. In each of our cases of gout, when metabolism was being studied in relation to the *x*-ray, the excretion was decreasing after an acute attack. It showed absolutely no increase, but actually continued to decrease when *x*-ray treatment started, and this was repeatedly observed afterward. The changes that are usually seen in metabolism in gout continued to be present in these cases, therefore, and the course was apparently undisturbed by exposure to *x*-rays.

The facts that have just been mentioned demonstrate, we think, that the effect is not a direct one but one that requires response on the part of the individual. It might certainly be anticipated that if any destructive action is exerted directly by the *x*-ray this action is more likely to occur with the tissues of a dying patient than with the tissues of one who is improving; but the patient that improved showed tissue destruction strikingly, while the patient that died showed none. This apparently cannot be explained in any way excepting upon the assumption that the patient that died was incapable of doing something that the other patient could do. The same explanation must be given for the fact that normal persons and leukemics who are improving show increase of nuclein metabolism and of general nitrogen metabolism, while our two patients with gout showed no effect. Only peculiarities in individuals can explain such results. This dependence of the favorable effect of *x*-rays upon individual reaction helps largely to explain the difference in the results in different cases. These differences are apparently not due so much to mere stubborn progress of the disease as they are to lack of that power in the individual which makes him capable of controlling the disease by responding to the stimulating action of the *x*-ray.

To be more specific concerning the processes that are stimulated and accelerated by the *x*-ray we consider that it is highly probable

that the action is chiefly upon autolysis. A considerable number of physiologic and pathologic body processes have, with great probability, been shown to be due to autolysis; that is, to activities that have the characters of ferment-like processes and that produce in their course the same classes of substances as those found in the various stages of digestion. The view is now widely accepted that the exudate in pneumonia undergoes resolution as a result of sudden autodigestion, carried out not through bacterial influence but through the activities of the tissues; the result in this case being due to a reaction that overcomes the effect of disease. In acute yellow atrophy and in phosphorus poisoning the liver, in particular, undergoes autodigestion, this being here apparently an important part of the progress of the disease. In involution of the puerperal uterus the excess of tissue is removed in this instance for purely physiologic purposes by the same sort of autodigestion. These are conspicuous examples of fairly firmly established facts, illustrating the physiologic and pathologic importance of autolytic functions. Analogy with these and with many other similar facts that have been determined has led to the belief that catabolism in general is a ferment-like or digestive process.

Following then the general trend of thought and the direction in which the results of recent experimental work pretty generally point, the most natural explanation of an increase in tissue destruction, when this increase is dependent upon individual body reaction, is that it is due to acceleration of autodigestive or autolytic processes. The remarkable suddenness and intensity with which the action of the *x*-ray begins immediately after exposure is more direct evidence in favor of the view that autolysis is influenced. This rapidity and intensity of action constitutes the most striking feature of the effect of *x*-rays upon metabolism. In our second leukemic case and in our normal subject nitrogen and uric acid excretion were immediately greatly increased as a result of only five to eight minutes' exposure to *x*-rays. Baermann and Linser also saw an immediate influence upon nitrogen metabolism, and Heile observed the same effect upon purin bases and uric acid. Heile seems not to have controlled the diet and

other factors, but this probably does not affect his results to any important degree. This extreme rapidity of action is a common feature with agents that influence ferments. It is also a most conspicuous feature in the resolution of pneumonia, in which disease the potential capacity to digest the exudate is apparently usually present, but is latent until some unknown factor causes it ordinarily to become suddenly active, and then within a brief time a large mass of exudate is dissolved and disappears. In the suddenness and intensity of the change that occurs the effect of *x*-rays is closely analogous to the resolution of pneumonia. Immediately after a brief exposure metabolism may proceed at double its previous pace or perhaps even more rapidly.

Finally, the analogy between the effect of radium and that of *x*-rays is so close that the probability that *x*-rays accelerate autolysis becomes nearly a certainty when one considers that Neuberg has demonstrated, *in vitro*, that radium has this influence.

The study of autolysis and derangements of autolysis has already acquired great physiologic and pathologic importance, and is certain to become vastly more important than it is now; and from the standpoint of treatment measures that seem to influence autolysis have a very noteworthy degree of interest, since they offer the possibility of devising scientific means of treating some of those diseases that have hitherto been managed largely, often indeed solely, by empirical methods.

One such condition that at once, after making our observations concerning the effect of *x*-rays on metabolism, suggested itself as perhaps suitable for *x*-ray treatment is unresolved pneumonia. Successful management of pneumonia is, of course, a combat, as a rule, chiefly with the toxemia of the disease rather than with the exudate or the effects of the exudate; consequently, measures that affect the exudate are not likely of themselves to influence very largely the mortality from the ordinary acute form of the disease.

x-rays have been used in the treatment of pneumonia, but without any definitely successful results. In unresolved pneumonia, however, the observations of Flexner indicate that the persistence of the exudate is due to the non-occurrence of the

autolytic processes that take place in cases that resolve. Rational treatment of unresolved pneumonia should in that case consist chiefly of measures that directly stimulate the autodigestive processes in the exudate, if such measures can be found; and the possible suitability of *x*-rays for this purpose is at once evident. It is only a possible suitability and not a certain one, even if it be granted, that *x*-rays act through influencing autolysis, for autolysis in the lung, in the liver, in the lymphatic tissues and in other body structures it is the same process only in its general nature. It differs in many tissues, and perhaps in all, in the characters of the ferments that carry on the digestive processes and in the products of these processes, and it is by no means certain that an agent that influences autolysis in one form of tissue, even if its effect there is most energetic, will have any influence upon autolysis in other tissues.

The possibility of a good effect seemed, however, sufficiently clear to lead us to use *x*-rays in the one suitable case of unresolved pneumonia that has presented itself since this idea was entertained.

The patient, a man aged sixty-seven years, was admitted to the Episcopal Hospital on the service of Dr. A. A. Stevens, on March 13, 1905, the third day of an acute pneumonia of the right upper lobe. Crisis occurred on March 20th. When first seen by Dr. Edsall, on April 1st, all acute symptoms except some exhaustion had long disappeared, but there was no sign of resolution. Slight local improvement gradually took place, but it was extremely slight, and on April 21st, when *x*-ray treatment was started, there was still marked dulness and bronchial or bronchovesicular breathing over the whole of the diseased lobe. *x*-ray exposures were given daily for four days, but were limited to five minutes' duration, lest any dangerous results should follow. The signs rapidly improved, and at the end of a week it would have been almost impossible to have determined by physical examination which side had been affected.

One case proves nothing, but this result is sufficiently suggestive to encourage further trial in other cases of unresolved pneumonia. If any good is to come of such treatment, however, it will prob-

ably be only in recent cases, for little effect could be expected in cases that have become organized. We may in this connection note that *x*-rays were also used in another case at the Episcopal Hospital in which there was an old consolidation at the left base, the duration of the pulmonary trouble being unknown and the cause not positively determinable. In this case there seemed to be absolutely no influence.

Since the effect of *x*-rays upon protein tissues is probably exerted upon the ferment processes that occur in those tissues it seemed worth while to study the effect of *x*-rays in diabetes. It is not at all clearly shown that sugar is broken down in the body by ferment processes, but in spite of the unconvincing results of experiments undertaken to prove this point it is extremely probable that it will ultimately be demonstrated; therefore, it seemed quite possible that diabetes would be favorably affected by *x*-rays through their action upon the hypothetic ferment-processes that are supposed to digest the sugar in the body fluids and tissues, just as leukemia seems to improve through the action of *x*-rays on ferment processes affecting protein. So far, however, as our observations have gone this is not the case. Two patients with diabetes, under the care of Dr. Edsall, were treated with *x*-rays, and in neither was there any appreciable effect. Both were severe and very unpromising cases, and it is possible that the hypothesis which led to the treatment was correct but that the disability of the patients was too great to permit of their responding to stimulation. It would not be at all surprising, however, if the *x*-ray had no effect upon carbohydrate ferment-processes, while exerting a lively influence upon some, or perhaps even all, protein ferment-processes, for various ferments are affected in a different manner by many chemical and physical measures.

The conditions that we have mentioned constitute only a fraction of the nutritional and infectious processes in which the effect of the *x*-rays might perhaps be profitably studied from this same standpoint, using both bedside and laboratory methods of investigation.

REFERENCES.

Albers-Schönberg. Münch. med. Woch., 1903, No. 43.
Heineke. Mittheilungen aus dem Grenzgebiete der Medizin und Chirurgie. Bd. xl., Heft 1 and 2.
Von Noorden. Lehrbuch der Pathologie des Stoffwechsels.
Magnus-Levy. Virchow's Archiv., Bd. clii.
Taylor. Contributions from the William Pepper Laboratory of Clinical Medicine, 1900.
Moraczewski. Virchow's Archiv., Bd. cli.
Baermann and Linser. Münch. med. Woch., 1904, No. 23.
Heile. Zeitschrift für klin. Medizin, 1904.
Neuberg. Zeitschrift für Krebsforschung, 1904.

DISCUSSION.

DR. WILLIAMS: I have been much interested in these papers and agree with Dr. Edsall. I wish, however, to make this suggestion. It is now possible to measure the dose of the *x*-rays by an instrument which corresponds to the instrument used to measure ordinary gas light (photometer). It seems to me that we cannot be too careful, and that we should remember that the dose of *x*-rays should be carefully determined, especially when one considers that sometimes the same tube may give several times the dose of the rays that it gives at other times, and particularly that some tubes give ten to twenty times as much as others.

DR. EWING: I should like to say a word in support of Dr. Edsall's conclusions regarding certain points of resemblance between leukemia and acute yellow atrophy.

In 1897, with Dr. W. H. Thomson, I reported a case of acute leukemia following pregnancy. I have since examined one other. The histologic condition of the liver in both these cases indicated that as far as hepatic metabolism is concerned the two diseases may reach a nearly identical stage. The development of leukemia following pregnancy, which is not infrequently reported in the literature, the fact that pregnancy is the most definite predisposing basis of acute yellow atrophy, and the similarity in the hepatic lesions and in the metabolic disturbances in these two diseases, suggests that there may be an identical etiologic factor in them. It would, however, be too much to say that they are in any essential respect identical in origin, since there are many conditions which may combine to produce the hepatic lesions now passing under the term acute yellow atrophy, but the hepatic lesions and chemistry of the urine indicate that these two morbid processes have much in common.

DR. BARKER: I have been very much impressed with the study and results of Dr. Edsall and Dr. Musser in connection with autolytic processes, espe-

cially with their comments upon the speed of the reaction which takes place. It seems remarkable that there should be so much variation, sometimes very slow speed, sometimes very great speed. These reactions may be largely a matter of catalysis. Since the theory of catalysis has been put on an experimental basis tremendous progress has been made in inorganic and organic chemistry. I cannot help but feel that the application of the doctrine of catalysis to physiologic experimentation is going to be very helpful. The general chemists have already worked out a large number of facts bearing on the subject. We know already many laws governing catalysis, and I hope that the processes of metabolism may soon come to be better understood by examining with the velocity of reactions and studying the positive and negative catalyzers in which their speed depends.

Dr. Edsall: In regard to Dr. Ewing's remarks, I should like it to be understood that I meant to make no suggestion concerning the morphologic conditions in acute leukemia as compared with those in acute yellow atrophy. I meant only to compare these two diseases in the fact that both cause great and rapid destruction of tissue.

I do not think I have been particularly bold in experimenting with *x*-rays. Most of the cases that I have mentioned were instances of disease that are at present being generally treated with the *x*-ray, and I think justifiably so; and in these cases, as well as in all others in which I have recently used the *x*-ray I have insisted upon beginning with a small dose, and only gradually and very carefully increasing the dose, watching all the time for possible evil effects. The lesions that Dr. Warthin and others have found should not, I think, frighten us into giving up the use of the *x*-ray. These lesions indicate the necessity for caution, of course, but I think they really indicate also that the *x*-rays are accomplishing the purpose for which they are being used. This is true, at any rate, in conditions such as leukemia and Hodgkin's disease.

I do not think that Dr. Barker's idea differs much from that which I expressed. I feel that the results that I have described show that the effect of the *x*-rays is the consequence of a reaction of the individual. I do not feel that it is possible to give a name to this reaction, except in a purely hypothetic manner.

REMARKS ON TREATMENT OF CARDIOSPASM BY NEW ESOPHAGEAL DILATOR.

By BERTRAM W. SIPPY, M.D.,
OF CHICAGO.

Idiopathic dilatation of the esophagus may be the result of the following conditions:

1. Primary spasm of the cardiac end of the esophagus (Meltzer and Mikulicz).
2. Primary atony of the muscular wall of the esophagus (Rosenheim).
3. Disease of the pneumogastric nerve (Kraus).
4. Esophagitis, with secondary spasm of cardiac orifice (Martin).
5. Congenital sacculation at the lower end of the esophagus (Fleiner).

Cardiospasm or spasmodic contracture of the lower end of the esophagus is by far the most common cause. In the case described by Dr. Billings this condition was present.

To relieve the spasm various means have been devised. In many cases in which the process is only slightly developed temporary and even permanent benefit may be obtained by appropriate diet, rest, the passage of bougies and the use of antispasmodic remedies. Experience, however, shows that when dilatation through the retention of food has become so great that the esophagus is large enough to contain 200 c.c. or over the trouble is likely to recur. The obstruction becomes more obstinate, the regurgitation of food increases, until finally death from inanition takes place unless radical measures are adopted. In most cases the nutrition may be maintained for a time by feeding through a stomach tube, but to continue this indefinitely

is extremely unsatisfactory, and owing to the irritability of the lower end of the esophagus it finally may be impossible to pass the tube into the stomach. In Dr. Billings' case one day the tube was arrested at the cardiac orifice, and nearly half an hour was consumed before the muscular fibres relaxed. The passage of a bougie in this case caused an increase in the spasm.

To overstretch the muscular fibres at the seat of the spasm is the best treatment as yet devised.

While large bougies give temporary relief in some cases no real stretching of the fibres at the seat of the stricture is accomplished. Rubber bags have been introduced into the stricture and then inflated with some degree of success. The principle of the urethral dilator has been utilized and long instruments constructed and used, as in the case reported to this Association last year by Dr. Tyson.

Mikulicz conceived the idea of making an opening through the stomach and then forcibly stretching the cardia from below by means of an instrument acting in the manner of a uterine dilator.

The success obtained by Mikulicz in the four cases thus treated by him has led others to adopt the same method. While the procedure is not particularly difficult or dangerous, it must be classed among the major operations.

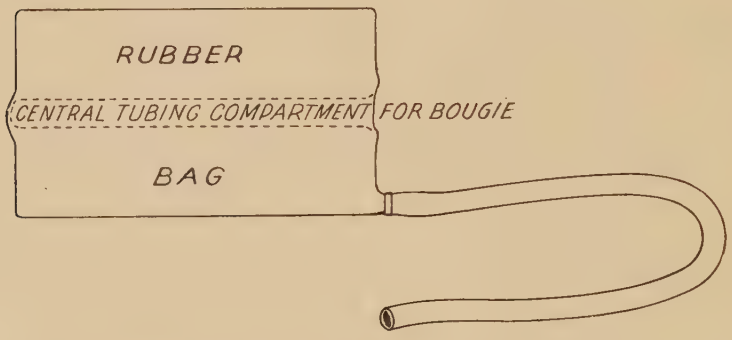
To obtain the same degree of dilatation safely and in a simple manner I have devised this instrument, which was used with happy results in the case described by Dr. Billings.

In its construction and use the rubber-bag idea has been elaborated, and an efficient dilator, absolutely under the control of the operator, is here presented.

The instrument consists of a rubber bag three inches long and one and a half inches wide when collapsed. At an upper corner of the bag a firm piece of rubber tubing, about twenty inches long, is attached. Another piece of small rubber tubing, three inches long, is secured in the centre of the rubber bag. The tip of a whalebone esophageal bougie is introduced into this compartment of the bag. The bougie guides the bag to the seat of the stricture.

The essential feature is a bag made of thin, firm cloth which surrounds the rubber bag, limiting accurately the degree of dila-

tation caused by distending the rubber bag with air. Without the use of the cloth bag the efficiency of the rubber bag as a dilator is greatly reduced. When introduced into the stricture and inflated the unprotected rubber bag expands toward the points of least resistance—*i. e.*, downward into the stomach and upward into the dilated portion of the esophagus, the stricture being only moderately stretched.



For that reason the use of the rubber bag dilator has heretofore been only partially successful. The cloth bag used in this case was so constructed that when the rubber bag was inflated a hard cylinder, three inches long and five and a half inches in circumference, was produced.

To prevent friction a rubber condom encloses the cloth bag. The collapsed bags, including the bougie, are no larger in diameter than an ordinary stomach tube. The bag is readily introduced into the stricture, and by using a firm rubber bulb it is quickly pumped full of air. The degree of pressure exerted is limited only by the strength of the air-pump and the cloth bag. It is obvious that great force may be directly applied to the stricture. The degree of dilatation produced is accurately controlled. The procedure is not painful.

In the case related by Dr. Billings the dilating force was applied only twice, an interval of three days intervening.

Note.—At the time of publication, five months later, there has been no return of the difficulty. Two additional cases have been as successfully treated in the same manner.

DISCUSSION.

Dr. Billings: Recently this mechanism has been used upon one of my patients in the Presbyterian Hospital who suffered from a typical cardiospasm with a dilatation of the esophagus. The measured contents of the dilated portion was 500 c.c. of water. There was marked spasm of the cardia, preventing the passage of a tube at times, and undoubtedly there was marked hypertrophy of the circular fibers of the cardia. The use of the instrument used by Dr. Sippy was followed after two applications by marked improvement. The patient is now able to swallow liquids and solids as she has not done for over two years.

INTESTINAL PERFORATION IN TYPHOID FEVER IN EARLY LIFE.

By J. P. CROZER GRIFFITH, M.D.,
CLINICAL PROFESSOR OF DISEASES OF CHILDREN AT THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

The occurrence of typhoidal perforation in children deserves consideration, first, on account of its supposed rarity, and, second, on account of the difficulty of recognition which is often presented and which seems to me to be largely peculiar to this time of life.

As to the *rarity* of its occurrence there appears to be little variation of opinion among many of the leading text-books. That the accident is uncommon, although just to how great an extent, is a matter regarding which statistics vary. Marfan[1] says that perforation in children is almost never observed. Baginski[2] speaks of it as uncommon, and has seen but 2 cases. Rotch[3] considers it exceedingly rare, and Holt[4] has found but 12 instances in 1028 reported cases of typhoid fever in children. As 4 are said to have recovered we are uncertain of the diagnosis in these. Heubner[5] has never seen a case. Wilson[6] considers it exceedingly rare, and Koplik[7] and Gerhardt-Seiffert[8] are of the same opinion. Henoch[9] has seen it but once in all his cases. Curschmann[10] speaks of perforation as rare in children.

On the other hand, Ashby and Wright[11] have met 4 cases, and Méry,[12] although admitting its great rarity, thinks that this has

1 Traité des maladies de l'enfance (Grancher, etc.), 1897, vol. i. p. 321).
2 Lehrb. der Kinderkr., 7 Auf., pp. 201, 211.
3 Pediatrics, 1901, p. 451.
4 Diseases of Infancy and Childhood, second edition, p. 1054.
5 Kinderheilk., vol. i. p. 508.
6 Cyclopedia of the Diseases of Children. Keating, vol. i. p. 408.
7 Diseases of Infancy and Childhood, p. 173.
8 Lehrbuch der Kinderkr., p. 175.
9 Kinderkrankheiten, 8 Auf., p. 780.
10 Nothnagel's Encyclopedia, p. 333.
11 Diseases of Children, second American edition, p. 283.
12 Traité des maladies de l'enfance (Grancher, etc.), second edition, vol. i. p. 495.

been somewhat exaggerated. He says that at least 14 or 15 cases have been reported from the Children's Hospitals of Paris during the last six years, quotes 26 perforations in 1506 cases collected by Setbon, and says that Murchison, in 73 reported perforations, found 10 in children under ten years of age and 8 in those from ten to fourteen years.

Journal literature, too, although in general speaking of the rarity of perforation in early life, gives somewhat varying statistics. Roemheld[1] found 3 perforations in 117 cases and Montmollin[2] reports 7 cases, 3 of which, however, recovered. Morse[3] reports no perforations in 234 cases and only 4 in 735 cases published by eight observers whom he quotes. Fitz[4] found 7 perforations among 192 children and Adams[5] 11 perforations in 337 cases. Rennert[6] gives 4 perforations out of 471 cases and Schulz[7] 8 cases of perforation in children.

One of the most valuable contributions to the subject is that of Elsberg.[8] Out of 289 collected cases of operation for perforation in typhoid fever 25 occurred in children less than fifteen years of age. He gives a useful analysis of the symptoms exhibited in these and concludes that they do not differ materially from those occurring in adult life. This article deals so thoroughly with the literature of the subject that it is not necessary to enter more fully upon it in this connection.

That typhoid perforation should occur less frequently than in adults is in accord with the characteristics of the lesions of the disease in early life. In the fetus typhoid ulceration is uniformly absent. In infants it is exceptional that it is at all extensive or severe. As age advances it grows more common, but is generally less frequent and less severe than in adult life. Nevertheless, very extensive ulceration can exceptionally occur even in early childhood, as I have seen proven upon the postmortem table. Consequently, the occasional development of perforation is to be expected as a

[1] Jahrb. f. Kinderheilk., vol. xlviii. p. 207.
[2] Thèse, Neuchatel, 1885.
[3] Boston Medical and Surgical Journal, Feb. 27, 1896.
[4] Transactions of the Association of American Physicians, 1891.
[5] Archives of Pediatrics, Feb., 1904.
[6] Deutsch. med. Wochen., 1889, p. 1063.
[7] Jahrb. der Hamburger Stadtskrankenanstalten, 1889, vol. i.
[8] Annals of Surgery, July, 1903.

matter of course, and the older the child the more liable is this to happen.

As my experience has been unfortunate in having met with 6 instances of perforation in children it may be of service to put these on record. The history of the first has been previously published, but is reported here for the sake of completeness of the group. The others I have not recorded heretofore, although the fact of their existence I had referred to in the discussion of a paper by Dr. J. H. Jopson.[1] The surgical aspects of the sixth case have been alluded to briefly by Martin and Pennington.[2] For various reasons none of the cases had a leukocyte count made when perforation was suspected. It is doubtful, however, whether this, if done, would have aided much in the diagnosis.

Case I.—Leila B., aged ten years, entered the Children's Hospital of Philadelphia, February 26, 1897, on about the sixth day of typhoid fever. During her first two weeks in the hospital she passed through an ordinary attack of the disease without abdominal pain or tenderness and without diarrhea until March 12th, when two watery movements occurred. On the evening of March 15th, approximately the twenty-third day of the disease, rather severe pain developed in the right iliac region, yet without signs of any serious trouble being present. The temperature had been approximately 104° unless reduced by tubbing. During the night slight intestinal hemorrhage occurred, with a fall of temperature to 103°. On the following day, March 16th, there was abdominal pain, not very severe, with slight distention of the abdomen, accompanied by tenderness and increased resistance. The pulse had lost in force, and the face had a somewhat anxious expression; yet there was no evidence whatever of collapse, the temperature remaining about the same. Later in the day vomiting began and continued troublesome. The abdomen was more distended and the hepatic dulness was nearly obliterated. The temperature had fallen in the evening to 101°. During the following night the abdomen became more distended and the child died in the early morning of March 17th, the temperature having fallen slowly to

[1] Archives of Pediatrics, March, 1904.

[2] American Medicine, Nov. 21, 1903.

99.6°. None of the ordinary symptoms of collapse had been exhibited at any time. The occurrence of a perforation had been suspected at the beginning, and later believed to be undoubted, but operation could not be performed—for reasons upon which it is not necessary to enter.

The autopsy showed a perforation of the ileum, about fifteen inches above the ileocecal valve, with extensive and deep ulceration of Peyer's patches.

Case II.—Charles K., aged eleven years, entered the Children's Hospital on February 28, 1899. He had been ill for four days with fever, malaise, chilly sensations, loose cough, and some pain in the abdomen and hips, "a kind of attack that he had frequently had before." An examination on March 3d showed a slight diminution of expansion of the left side of the chest, with dulness on percussion from the sixth rib downward in front and in the axilla; somewhat feeble respiration and some friction sounds on deep inspiration. Posteriorly there was dulness on percussion over the lower third of the left lung. The spleen could not be felt. The diagnosis of pleurisy or of pleuropneumonia was made.

The boy continued to do well, the temperature remaining elevated from 100° to 103°, and the bowels, at first normal, becoming diarrheal in character. On the afternoon of March 6th, his seventh day in the hospital, and apparently his eleventh day of illness, he complained of pain in the abdomen and vomited. The symptoms were apparently the result of his having eaten some ice-cream. Vomiting continued all night and general weakness developed, with feeble pulse, sufficient to make hypodermic stimulation necessary. The temperature arose in the mean time to 105.8° without any previous fall of it. March 7th found him with constant vomiting, a cold and clammy skin and general abdominal distention, tenderness and pain. The friction sounds over the lung were less numerous. The condition continued all day, the cause of it being not at all understood. His temperature ranged from 102° to 105°. On March 8th he was better, but the features were quite sunken. The abdomen was less distended, but very tender, and the hepatic dulness not at all diminished. The dulness over the base of the left lung had disappeared. A few small rose spots were

discovered on the trunk, suspiciously like the typhoid roseola. There appeared to be some increase of resistance in the right iliac region. The temperature was 106° in the morning of this day and 100.6° in the evening. The existence of typhoid fever was now suspected for the first time, and it seemed very certain that perforation had occurred. No operation could be performed.

At 3 A.M. on the morning of March 9th the temperature dropped to 97.8°, but quickly rose, and at 7 o'clock A.M. it was 101.2°. Failure of strength continued; on March 10th there were sunken features, jactitation, a tense and moderately distended abdomen and a greater resistance to palpation of the right iliac fossa. The temperature in the morning was 105.4°, but fell to 102.4° in the evening, when death occurred.

Autopsy showed a general purulent peritonitis; a perforation in the ileum five inches above the ileocecal valve; other ulcers in the ileum, some apparently in process of healing; evidences of quite recent pleurisy over the right lung, and some soft adhesions over the base of the left lung.

It was evident from the autopsy that the disease was farther advanced than the history indicated, and that the child had been a case of walking typhoid, complicated later by pleurisy.

CASE III.—Celia S., aged twelve years, first seen in consultation with Dr. S. N. Dubin May 1, 1899. The child was at the time apparently in the fourth week of typhoid fever. Her mind had been clear and her condition good throughout, except for constant tendency to hyperpyrexia still existing, the temperature being often 106° or over. The tongue was moist and there were slight tremulousness and moderate diarrhea. By May 4th her condition was much the same, except that the diarrhea had nearly ceased. There was, however, retching when food was given. Later, vomiting began again, but was only occasional, and the child's condition continued no worse. There were at times specks of blood in the stools. At five o'clock on the morning of May 9th she suffered from sudden severe abdominal pains and a fall of temperature from nearly 107° to 97°. Dr. Dubin felt certain that she had a perforation. I was asked to see her again, and did so in the afternoon, but failed to meet Dr. Dubin, who was unavoidably detained.

She had at this time moderate abdominal tenderness on pressure, but no distention or vomiting, and no evidence whatever of collapse or any noteworthy abdominal pain. Her temperature was still elevated. I had heard nothing of her suspicious symptoms, and careful questioning of the parents, who were rather ignorant people, failed to elicit any history of their previous presence. The indications of perforation returned later, and she was removed, on May 10th, to the Methodist Hospital, where I saw her again in consultation with Dr. Dubin and Dr. E. W. Holmes, the attending surgeon. She was now clearly very ill, and her mind was partly clouded. Operation was done at 10 P.M., about forty-one hours after the first symptoms appeared. A perforation was found in the ileum, with several ulcers threatening rupture. Death occurred before morning.

CASE IV.—Frank M., aged eight years, was admitted to the Children's Hospital of Philadelphia January 2, 1903, apparently at the end of the first week of typhoid fever, having suffered from loss of appetite, malaise, slight cough, headache and slight abdominal pain. Examination showed the child emaciated to some extent, the heart normal, a few rales in the lungs, the spleen indistinctly felt, rose spots present on the abdomen and slight gaseous distention. His condition continued fairly good, there being very slight diarrhea, and the temperature running from 102° to 104° or 105° and making hydrotherapy necessary. On January 14th, the thirteenth day of his stay in the hospital, he was still doing well, although having a rather severe attack of the disease; but at 11.30 P.M. vomiting occurred, the temperature being 104°, and continuing from this to 105° during the night. On the morning of the 15th his pulse was weak and irregular and his abdomen moderately distended and only slightly painful on pressure, but extremely tense. The hepatic dulness was normal. There seemed to have been no sudden development of this condition, and his temperature did not fall below 101.2° on this date. He vomited again at 9.45 A.M. and at 11.30 A.M. The possibility of a perforation having occurred was considered, but the absence of any evidence of collapse and the slight degree of vomiting and abdominal tenderness and distention, combined with the presence of normal

hepatic dulness, made it seem doubtful. There was, however, a suspiciously anxious expression of face. Request was left that Dr. R. Le Conte, the surgeon on duty, examine him when he made his visit, and a message was sent to his parents asking permission to operate if necessary. The child's symptoms grew worse so rapidly that a few hours made the diagnosis practically certain. The distention of the abdomen increased greatly, as did rigidity and tenderness, the liver dulness disappeared, abdominal pain became extreme and continuous, vomiting returned and occurred repeatedly and the features grew very much sunken. The temperature continued at about 103°, but diminished to 100.4° in the afternoon. Operative interference was absolutely refused by the parents, who removed the child on the following day, January 16th, against advice. He died on January 17th.

Although no autopsy was held there can be no reasonable question of the diagnosis.

CASE V.—Mary B., aged four years, was admitted to the Children's Hospital of Philadelphia March 8, 1903. Ten days previously she had commenced to suffer from loss of appetite, malaise, headache, diarrhea and epigastric tenderness or pain. After a short time the parents noticed that she had fever, and she was then put to bed. During the last three days the temperature had reached 104° and the other symptoms had continued. On admission she exhibited some distention of the abdomen, enlargement of the spleen, roseola and a coated tongue. The mind was clear; the Widal reaction was positive. She was considered to be probably in the middle of the second week of the disease. The attack ran rather a mild course, the abdomen showing considerable tympanitic distention, the child looking bright and the temperature gradually falling. By March 17th, the last occasion on which I saw her, the patient was convalescent, the temperature having been nearly normal most of the time for a week. I give a synopsis of the ward notes made after this date: At 7 A.M. on the morning of March 18th the child vomited food and medicine and had slight abdominal pain, but her temperature remained at 99° and she did not look ill. At 9.15 A.M. she appeared feverish and vomited again. At noon her temperature was 100°. There was no ab-

dominal pain, distention or tenderness and the child was sitting up in bed in apparently good condition. At 3 P.M. the temperature was about 103° and there were still no abdominal symptoms.

Shortly after this she vomited again twice, at 3.15 and at 4 P.M. At 6 P.M. the temperature was 105.6°. The mind was clear, but the child looked ill and was somewhat restless. There was no abdominal distention or pain. By 9 P.M. the temperature had risen to 106.6°, the child was growing rapidly worse and died at six o'clock on the morning of March 19th. Distention, pain and tenderness of the abdomen had continued to be absent, and there had been no return of vomiting since four o'clock on the preceding afternoon.

The autopsy showed a purulent peritonitis. The ileum exhibited numerous small ulcers near the ileocæcal valve, and in one of these was a minute perforation. The serous layer of the intestine at this point was adherent to another knuckle of the gut, thus partially closing the perforation.

CASE VI.—Esther S., aged six years, seen in consultation with Dr. Joseph Neff April 4, 1903. The child was presumably in the second week of typhoid fever. Rose spots were present. The general condition had been good. About four o'clock in the afternoon of this day she had suffered from quite severe abdominal pain followed by vomiting, and was said to have had decided depression of strength, although without actual collapse. It is not known whether there was any fall of temperature. I saw her at 10 P.M. and found her in excellent general condition, with the pulse of good quality, no anxious expression of face, slight diarrhea, no abdominal pain, tenderness only on firm pressure and distention only slight. Vomiting had ceased. The diagnosis of a perforation was considered, but dismissed as too uncertain to warrant operation.

I therefore advised cautious delay, but immediate operation should any of the symptoms return. A telephone message at 9 A.M. on the next day, April 5th, told me that the child had had a good night, that there had been no return of pain or vomiting, and that the abdomen was not distended or tender. Later in the morning, however, at about eleven o'clock, abdominal pain returned, distention became decided and the child was removed

to the surgical ward of the hospital of the University of Pennsylvania. Here the symptoms continued, perforation was suspected and operation was done by Dr. Edward Martin at about 5 P.M. in the afternoon of the same day. One perforation was found and two ulcers threatening rupture. The child was in bad condition immediately after the operation, but by the next day all symptoms were favorable. She did well for a time, but evidences of the formation of a pus cavity developed, and, although this was found and evacuated, her strength failed and death occurred seven days after the first operation.

I have referred in opening the subject to the difficulty in the recognition of perforation frequently exhibited in early life. Some of the cases here reported possessed the classical symptoms as usually seen in adults; others certainly illustrated the difficulty to which reference has been made. Case I., although exhibiting abdominal pain, tenderness and distention, had at first no more of these than is common in cases of typhoid fever with tympanites. There was no initial fall of temperature or evidence of collapse. The symptoms as exhibited could be called suspicious only. Later in the same day I should certainly have advised operation had it been possible to have had it performed, as there was reason to believe that perforation was probably present.

Case II. was absolutely misleading throughout. Even the presence of typhoid fever was not suspected. The child was supposed to be suffering from pleurisy only. The occurrence of vomiting and abdominal pain seemed clearly connected with an indiscretion in diet. It was only on the day following that on which perforation probably occurred that the suspicion arose that something more was ailing him, and not until the succeeding day that the diagnosis of typhoid fever and perforative peritonitis was entertained. The symptoms by this time were sufficiently positive to make operation urgent, although even now the abdominal distention was not great, the only fall of temperature below normal having occurred after the perforation had existed, probably, over two days.

A most unfortunate circumstance prevented a better understanding of the symptoms in Case III. Those at the onset were

clearly those of perforations, or possibly of concealed hemorrhage. The failure of blood to appear later in any large quantity in the stools excluded the latter. Within a few hours all symptoms had disappeared to such an extent that, although entertaining the thought of the presence of perforation, based upon the existence of some abdominal tenderness, I did not feel warranted in believing that this had occurred. Had I known of the earlier condition I should, of course, have advised immediate operation.

Case IV. presented doubt only during the first hours of the condition. There was at that time no history of collapse and no more abdominal distention, pain and tenderness than is very frequently present in cases of typhoid fever. There was also no loss of hepatic dulness. The earliest really suspicious symptom was alteration of the facies. In a few hours the symptoms were beyond question.

It is difficult to say in Case V. on what a diagnosis of perforation could possibly have been based. The vomiting was only occasional; the complaint of pain had been temporary and not great. There was no collapse, and throughout the twenty-three hours which followed until death occurred there was neither abdominal tenderness, distention nor pain to guide us. The count of the leukocytes might have been of significance if there had been any suspicion of what ailed the child, but even this is by no means certain.

Case VI. presented elements of great uncertainty. In view of the fact that vomiting and abdominal tenderness and pain are of such frequent occurrence in typhoid fever, I could not feel warranted in making a diagnosis of perforation or in advising exploratory laparotomy, especially when the symptoms had been unattended by any certain evidence of collapse and had so largely disappeared at the time of my visit. In any similar case I should, I think, again follow exactly the course taken in this—viz., delay cautiously until a diagnosis of perforation was more probable. From the point of view of the immediate results of the operation the child did well. Death occurred rather from a sequel.

DISCUSSION.

DR. JACOBI: I have nothing to contribute to the discussion. I would only say this: From what little I have seen the difficulty is so much the greater because now and then we find perforation without even a diarrhea having preceded the perforation through the whole course of the disease. I have seen perforation where, through the whole course of the disease, there was not a single attack of diarrhea, and so diagnosis certainly must be very difficult and certainly impossible in a great many cases.

DR. PEABODY: I don't think we should look for diarrhea as an aid to diagnosis. It is the rule rather than the exception to see cases in which perforation occurs without diarrhea, the patient having been constipated throughout their course.

HEMATEMESIS FROM GASTRIC ULCER; NOTES ON OVER TWO HUNDRED CASES.

By W. GILMAN THOMPSON, M.D.,
OF NEW YORK.

The present inquiry was undertaken with the view of formulating the indications for operation in cases of gastric ulcer. The cases have been collected from the records of the Presbyterian and Bellevue Hospitals, and from private sources, numbering collectively more than 200.

During the past sixteen years there have been treated at the Presbyterian Hospital 195 cases in which the diagnosis of gastric ulcer has been made, including 167 females and 28 males—a proportion of 6 to 1.

The most interesting feature of these cases is the fact that so large a number, considerably more than one-half, were discharged as "cured" after serious hematemesis, which occurred either immediately before admission or during the patient's stay in the hospital, or both. The exact figures are as follows:

Hematemesis: "Cured" under medical treatment	111
Improved " "	19
Unimproved " "	3
Died " "	41
Melena without hematemesis	1
Ulcer without hematemesis (cured)	20
	195

The total deaths, numbering 41, present a ratio of 1 death to 4.8 cases. Included in the deaths which took place among the unoperated cases were several in which the ulcer was not the whole cause; thus half-a-dozen patients died from pneumonia, 1 with abscess of the pancreas, 1 with pyonephrosis, 1 with pyopneumothorax, and 3 with a subphrenic abscess. One patient had a gastroureteral

fistula. In 8 of the unoperated cases and in 3 of the 20 which were operated upon, the patients died from the immediate effects of hemorrhage into the stomach, which was found at autopsy filled with blood. In 1 case, for example, the patient lost eighty ounces of blood by actual measurement during the three days that she was in the hospital prior to operation. That such a patient should die upon the operating table is no surprise, although the question might be raised as to the propriety of operating at all, for the situation is very nearly as desperate as operating for a ruptured aneurysm.

Twenty cases were transferred to the surgical division of the hospital for operation, of which 14 proved fatal and 6 were discharged as "cured." Of the 14 fatal cases, 4 presented a septic peritonitis from perforation, and were nearly moribund at the time of operation. Another, as stated above, was moribund from hemorrhage, a sixth was found to have a perforated duodenal (not gastric) ulcer, and a seventh proved fatal on the thirteenth day, a recent perforation having been disclosed at operation. No one of these 7 cases should, therefore, be considered as having any real bearing upon the operative treatment of gastric ulcer, for they all presented a forlorn hope, 2 patients dying on the table and 4 within twenty-four hours.

Among the 7 other deaths one was quite unaccountable. The patient, an Irishwoman, twenty-eight years of age, gave an acute history, including much gastric pain, hematemesis and melena. She had had serious gastric hemorrhage the day before the operation, which revealed nothing abnormal. The stomach appeared normal in size; there was no cicatrix, no visible ulcer and no hemorrhage. She rallied from the anesthetic, but died within twenty-four hours with a temperature of 105°. The cause of death, unless it was shock, with unusual temperature, could not be determined. Another patient proved to have a general tuberculous gastritis with hemorrhage. She also died within twenty-four hours. (This case was reported to this Association by F. P. Kinnicutt in 1902.) Another patient died from shock within twenty-four hours after operation. She had been in the hospital a year before for hematemesis, from which she was discharged "cured."

It appears that among the 20 operated cases the medical diagnosis was erroneous five times, there being 1 case of tuberculosis

of the stomach, 1 of perforating duodenal ulcer and 3 in which no ulcer was discoverable. From a further analysis of these 195 cases it appears that operative measures can rarely be relied upon for the cure of active hematemesis, and that also in many cases operation was delayed until the conditions present were too serious to admit of recovery. When successful results are to be anticipated they are to be looked for in the category of cases with adhesions, cicatrices and stenosis chiefly, and in operation such as gastro-enterostomy performed between, rather than during, attacks of hematemesis. In 2 private cases the only operation consisted in separating adhesions which bound the base of an ulcer near the pylorus to adjacent structures (the pancreas, intestine, etc.), and the stomach was not opened. Both patients have remained in the best of health, one for five and one for four years. One is a woman, forty-eight years, of age, who, four years prior to operation, nearly lost her life through excessive hematemesis, and suffered constantly thereafter from gastric pain and distress, with almost constant nausea and frequent vomiting. She refused my entreaties to submit to operation until she was so feeble as to make it a last hope, and she so nearly died upon the table that gastroenterostomy was not performed. The adhesions covered the base of an enormous ulcer, 5 by 3 inches across, and bound the stomach to the diaphragm and duodenum. For several days after operation violent hematemesis occurred, but none has taken place since, and, as stated above, the patient at present, after five years, is in robust health, eating any sort of food in reason. Prior to operation, for a long time, I was able to distinguish two varieties of pain, one apparently referable to the ulcer, and another which appeared to be due to adhesions, and was excited by peristalsis induced by natural movement of the bowels and catharsis, by forced diaphragmatic movements, and by manipulations of the thin abdominal wall, especially by coughing while deep abdominal pressure was made against the diaphragm. The operation proved the correctness of this distinction, one which I have been able to make in several other cases. A third case was that of a woman who had been under my observation for half-a-dozen years with symptoms of moderate gastric dilatation. She never at any time presented any of the symptoms of gastric ulcer,

yet when a gastroenterostomy was performed the cause of the dilatation was found to consist in a pyloric ulcer with cicatrization, which greatly narrowed the orifice. I will cite only two other personal cases in illustration of the difficulties which may attend diagnosis of gastric ulcer, even in the presence of hematemesis. In one of these cases the patient was operated upon for persistent hematemesis with a typical history of gastric ulcer. A small peptic ulcer $\frac{3}{4}$ inch in diameter was found near the pylorus, bleeding actively from its round periphery; considerable blood was also found in the stomach; the ulcer was excised and the patient made a complete recovery. The other case in contrast was clinically even more complete, yet the operation revealed nothing. The patient, a woman thirty-eight years of age, gave a classical history of gastric pain, epigastric tenderness, distress after eating, repeated attacks of hematemesis, with increasing weakness and emaciation, symptoms which lasted through many months. During a fortnight's stay in the ward the patient had serious attacks of hematemesis, and as there was no improvement under medical treatment, I advised operation. The stomach was opened and the surgeon who operated explored the interior thoroughly with an electric light; the mucosa appeared slightly granular and congested, but there was no hemorrhage, no cicatrix and no sign of any ulcer. The incision was therefore closed and the patient died three days later from exhaustion following repeated vomiting. Hence, it sometimes happens that diagnosis of the *exact* condition is extremely difficult as between hemorrhage from a circumscribed ulcer which may be cured by operation and that from a generally congested mucosa which may not be so cured. In none of the cases cited in this study has the chemical analysis of gastric contents proved of determining value, for the results have been too variable, not rarely in the same patient on successive days ranging from anacidity to hyperacidity. Additional difficulty is encountered in the variability and inconstancy of all the so-called "cardinal symptoms," and in fact that any one symptom, such as pain, vomiting or tenderness which has been present steadily for a long time, may spontaneously disappear or give place to another.

I am not yet prepared to accept a definite clinical classification of

gastric ulcer into acute and chronic types based upon hematemesis, as attempted by Moynihan, Samuel and W. Soltan and others.

This classification is based chiefly upon the fact that a number of cases occur in which there is a sudden single hemorrhage followed by complete and permanent recovery under medical treatment, whereas, with chronic ulcers there may be repeated small or large hemorrhages and other gastric symptoms recurring at intervals through months or years. Of course, if a patient has a single severe hemorrhage, without protracted previous symptoms, and never has any further symptoms after recovery, the case may be styled "acute," but many chronic cases of which I have records begin in this acute manner. One of the operated personal cases described above was of this type. Again, there may be no hemorrhage and the patient may yet die of perforation.

For these and similar reasons it does not appeal to me to accept a hematemetic basis of classification. In other words, a single large hemorrhage may denote a chronic ulcer, equally with an acute one. After all, the important difficulty lies not in trying to separate the gross ulcers into varieties, but in differentiating such cases as the three operated upon at the Presbyterian Hospital in which no gross lesion was found, *i. e.*, the cases of diffuse punctate hemorrhage. These cases suggest those of early hemoptysis without discoverable bronchial ulceration, and the early hemorrhage of typhoid fever which arises during the congestive stage, before the ulcers are well defined. They also resemble those cases of hematemesis which result from congestion in chronic endocarditis and hepatic cirrhosis with portal obstruction, yet no such accompanying lesions are found to explain them.

I have not attempted to trace the after-history of the patients who were discharged from the hospital as "cured" cases of hematemesis, for owing to the peculiar social conditions existing in New York this is well-nigh impossible. The great majority of hospital cases occur among young women, many of them foreigners, who belong to the social order of domestic servants, seamstresses, factory, operatives, etc. They constitute a floating population to a large extent, and are constantly changing their address, for the servants change their employers, and others rarely occupy the same lodg-

ings for more than one or two consecutive years. If a subsequent attack of hematemesis occurs, the patient is quite likely to go to a different hospital, nearer perhaps to a changed residence. It would not be possible to trace successfully the after-history of more than 10 per cent. of this series, which extends over a period of sixteen years, and partial statistics of this sort are decidedly misleading.

A better result is obtained, I think, by reviewing the past records derived from the patients on admission to the hospital, many of whom give a history of repeated attacks extending over a period from one or two, to a half-dozen years or more, showing that a complete or permanent cure is comparatively rare. Among the cases discharged as "cured" were some in which repeated hematemesis had occurred during five to six years

To estimate the mortality of gastric ulcer by statistical methods is liable to misinterpretation. For example, J. W. Russell[1] states that 42.6 per cent. of patients recover.

To say that more than 55 per cent. of patients with hematemesis received into the Presbyterian Hospital (111 cases out of 195) were discharged as "cured" is of little prognostic significance, for they might nearly all die within from one to six years of hemorrhage, perforation or other complications, and I do not think any patient should be regarded as "cured" unless an interval of at least five years of health shall have followed the attack, and even in such cases the diagnosis may have been wrong, and the original hemorrhage due to congestion, punctate erosions, chlorotic anemia or other cause, and not to peptic ulcer.

It is admitted that the cases studied for this review do not appear perhaps to make a very strong argument in favor of operation, but many came under operation too late, and most were operated upon before the recent advances in the technique of gastric surgery.

On the other hand, a total fatality of 41 cases among 195 and a possible much larger mortality among those which have not yet run their course, should constitute a plea for earlier surgical intervention in fairly typical cases.

The mortality from cases of gastroenterostomy for gastric ulcer appears to be gradually lessening under improved technique.

[1] Lancet, January 30, 1904.

Thus, in 1897 von Mikulicz[1] gave it as 16.1 per cent. for 238 collected cases, and in 1900 Mayo-Robson[2] gave practically the same figure, 16.4 per cent. for 188 collected cases, for all complications except active hemorrhage and perforation, and a year later the mortality rate for his own cases was only 5 per cent. B. G. A. Moynihan's[3] figures are 153 gastroenterostomies for ulcer with only 2 deaths, and in 22 cases of gastric hemorrhage which apparently would have soon proved fatal there were 19 recoveries after operation.

Joseph A. Blake, in an article upon "The Surgical Treatment of Gastric Ulcer," published December, 1904, in the *American Journal of the Medical Sciences*, states his opinion "that a single large hemorrhage, without previous symptoms referable to ulcer, should not be operated upon, but when there have been antecedent symptoms operation should be performed." Also, that " cases suffering from a recurrent hemorrhage should be operated upon."

In these views I concur and would add that those chronic cases also should be operated upon in which the patient's life is either made miserable through pain or endangered through persistent vomiting and emaciation, provided medical treatment tried for two or three weeks has failed to produce any improvement. Let the surgeon be given the advantage of dealing with cases not already made almost hopeless through anemia, ulcers on the verge of perforation or complicated by a mass of perigastric adhesions. To offset these grave dangers early operation (gastroenterostomy) offers freedom from further hemorrhage, from chronic hyperacidity, pain, traumatic irritation of the ulcer by food, motor insufficiency and gastric dilatation. Blake makes the further assertion that in the early operative cases the patient may be subjected to less shock than in most cases of appendicitis.

Some additional data derived from a series of 107 cases occurring during the past eight years may be of interest as bearing more or less directly upon the subject and the possibilities of operative interference. Although the ages of the patients range from seventeen

[1] Centralbl. f. Chirurgie, 1902, 1897, p. 69.
[2] Philadelphia Medical Journal, May 25, 1901, p. 1005.
[3] British Medical Journal, April 8, 1905.

to sixty-nine years, 51, or nearly one-half of this series, occurred between the twentieth and thirtieth year, and were observed as follows:

Seventeen to twenty years, 10 cases; twenty to thirty years, 51 cases; thirty to forty years, 34 cases; forty to fifty years, 7 cases; fifty to sixty years, 5 cases.

Of the 28 cases among males, more than one-fourth occurred among those whose occupations predispose to metal poisoning. Thus there were 3 coppersmiths, 2 printers, 3 painters, and 1 pianomaker. All but 8 were more than thirty years of age. Some years ago I lost a patient from foudroyant hematemesis, a man forty years of age, who for three years had taken large quantities of arsenic. A physician had prescribed it for chronic acne and eczema, and the patient, unaware of its baneful effect, had continued its daily use upon his own responsibility. The hemorrhage was the only symptom of ulcer, but it proved fatal during one night and I attributed it to a probable ulcer from this form of metal poisoning.

To the above list of 195 cases may be added 6 which occurred in Bellevue Hospital during the past year, of which 3 were males and 3 females. Of these 1 was cured, 1 improved, 1 died of hemorrhage, and 3 were unimproved—all had hematemesis. The ages of the three males were respectively forty, forty-one, and fifty-one years. In January of this year two more cases occurred among males.

One patient, thirty-six years of age, was discharged improved after hematemesis, and one fifty-four years of age died after operation with perforation of pyloric ulcer. He had no hemorrhage at any time (he was a painter).

(The 8 cases, added to the previous 195, make a total of 203 hospital cases.)

The influence of social status upon the etiology of gastric ulcer is well exemplified in a comparison of the records of Bellevue and the Presbyterian Hospitals for the year 1904. In Bellevue, with 17,765 medical cases treated during that year, there were only 6 cases of gastric ulcer in the entire service, one of the four divisions having none at all—approximately 1 case in 3,000. In the Presby-

terian Hospital, with 1218 medical cases treated, there were 15 of gastric ulcer, a proportion of 1 case in 80. In Bellevue, with 7595 surgical cases treated, but one operation was performed for gastric ulcer (which proved to be a complication of carcinoma), against 1925 operated cases in the Presbyterian Hospital, with 4 for gastric ulcer. The majority of gastric ulcers occur among the servant girl and seamstress class, patients who are more likely to seek private than municipal hospital relief, either from a species of natural selection or because their well-to-do employers are in the habit of contributing to the financial aid of private hospitals; hence they become interested in them and refer their dependents to them. The municipal Bellevue Hospital abounds in cases of alcoholic gastritis, gastric carcinoma, syphilis, arteriosclerosis, privation and starvation, yet these prove to be comparatively infrequent etiologic factors. There were 144 cases classed as "gastritis" in Bellevue in 1904. What is there in the dietetic or other habits of life of the serving woman class that predisposes to this definite lesion of the stomach wall? It can hardly be their frequent diet of tea and toast, nor tight lacing (Rasmussen); yet what is it? I raise the question as an interesting one, but cannot answer it.

I have examined also the records of cases treated at the Cornell Dispensary since its foundation five years ago. There have been in the General Medicine Clinic alone 13,500 cases, with only one of gastric ulcer—a male, a metal polisher, forty-nine years of age. He had had gastric symptoms for eight months, including hematemesis. I was greatly surprised by these data, the more so because Dr. William Armstrong, of my staff, who has for several years devoted his time to making analyses of stomach contents as an aid to diagnosis, reports that among 150 cases lately studied in the clinic he has not once been enabled to make the diagnosis of gastric ulcer.

These data are of interest in showing the relative frequency of occurrence of gastric ulcer among certain classes of the community.

DISCUSSION.

Dr. Kinnicutt: It seems important to bear in mind in advising operative procedure how frequently it occurs that the affected area is not discovered; that is, even where the greater portion of the stomach is freely accessible to examination. The ulcer may be extremely small and require the most diligent search to find it. No examination could be made in the ordinary surgical operation which would be sufficient. I am reminded of this from having seen a case of Drs. Weir and Abbe, in which the patient died from hemorrhage. Operation was refused by the patient. After death it required the most searching examination to reveal the ulcer. It was hardly larger than a pin-head, but it had perforated into a large vessel.

The second point I should make is this: Frequently in cases where one or several successive hemorrhages have been of a very profuse character, and death seems imminent, the hemorrhage suddenly ceases and that is the end of it. These patients recover and will go a number of years without further symptoms. I think we have all had this experience. In the past winter a patient was sent into my hospital wards for operation. Within a few hours the immediate effects of the hemorrhage abated and the surgeons concluded to wait a little longer before operating. Hemorrhages had been occurring at intervals of a few hours for several days. The patient made a good recovery under the usual therapeutic measures. No matter how imminent death seems from hemorrhage, it is always possible that it is the last hemorrhage, in the sense that the patients recover, not die. This is not contraverting Dr. Thompson's views in regard to the advisability of operation for hemorrhage, but it suggests that an unfavorable prognosis, even in very grave cases without operation, is not always warranted. In advising operative interference the possible after-effects in the way of stenosis from cicatricial contraction should be borne in mind.

Dr. Cohen: The possibility of the recurrence of gastric ulcer in new situations after operation is not to be overlooked. We have not the data for a sufficiently long time to be able to make definite comparisons with the frequency of recurrences after recovery under non-operative treatment. It is sometimes very difficult to determine the propriety of operation. A patient under my care at the Philadelphia Hospital—and this bears out a point made by Dr. Thompson in regard to diagnosis in cases of very recent profuse hemorrhage—a carpenter, advanced in years, had sudden profuse gastric hemorrhage without pain. No significant precedent symptom of any kind could be learned from the patient or from his friends. I diagnosticated probable ulcer, however, and sought surgical advice at once. The surgeon considered the patient too weak to survive operation. We decided to wait and watch. The patient

improved so much that the surgeons now decided against the necessity for operation. Suddenly a second hemorrhage occurred without warning and autopsy was the next procedure. There were numerous erosions and some twenty or thirty actual ulcers of various sizes, all but two of which had healed. Death occurred by hemorrhage from the largest and probably latest ulcer. The history gave no clue to the presence of this multiple ulceration that had gone on for many years. It is possible that the patient had paid little attention to vague epigastric discomfort. Operation at a favorable time might have postponed death here. On the other hand, I recall the case of a young lady who was under my care seventeen or eighteen years ago, with gastric hemorrhage diagnosticated as probably ulcerative, and who recovered under medicinal treatment. Recently I was sent for again and found all the symptoms of gastric ulcer, but without hemorrhage. I suggested operation, but was immediately met by the objection that she had recovered without operation from what seemed a more dangerous condition so many years ago. The patient is again apparently recovering under medicinal measures. Would operation in the first instance have prevented the present recurrence? There seems a good deal to be said on both sides of this question. This also brings to mind another case illustrating the vagaries of gastric ulcer.

A girl was brought into my ward in the Jefferson Hospital suffering with symptoms pointing to the gall-bladder, fever, colic, pain, vomiting, and local tenderness. There was no hematemesis. Evidently the case required surgical exploration. My colleague, Dr. J. Chalmers Da Costa, operated upon her after consultation, and we found a recent gastric ulcer almost on the point of perforation. The pain and tenderness, however, were not due to the existing ulcer, but to adhesions between the stomach and the gall-bladder at the site of previous ulcers, which had evidently healed without giving rise to dangerous symptoms. We are not yet in position to draw dogmatic conclusions as to the long-run results of medicinal or surgical treatment, or even spontaneous recovery. My view of course, in considering all the evidence, is entirely in accord with the reader of the paper that, when we can make the diagnosis, surgical measures should be instituted as early as possible.

Dr. Sippy: In many cases it is exceedingly difficult to decide when operative treatment is indicated to control hemorrhage from gastric ulcer. As a rule, the first hemorrhage does not destroy life. When a bloodvessel of sufficient size to cause fatal hemorrhage is eroded death usually takes place before surgical aid is obtained. If a second severe hemorrhage occurs within a few hours or days gastroenterostomy should be seriously considered.

In another class of cases operation is clearly indicated provided proper medical measures have been instituted. I refer to cases in which there may be no hematemesis, but chemical analysis of the stool shows that blood is constantly oozing from the ulcer to such an extent that anemia is developing toward the danger point. Surgical treatment should be adopted before the

hemoglobin has been reduced to 40 per cent. If the reduction in hemoglobin has taken place relatively rapidly it is very probable that operation may be permitted, even in cases in which the hemoglobin has been reduced below 40 per cent.

I recently observed a girl, aged nineteen years, that had lost blood from repeated hemorrhage during a period of two weeks. The hemoglobin registered 20 per cent. In that case I deemed surgical interference contraindicated. She fortunately made a good recovery. It is very probable that operation in her reduced state would have proved fatal. It is in such cases, and in those in which anemia approaching that degree has already been reached, that the advice to operate must be given with extreme caution.

It is a good thing to remember that under proper medical management a certain percentage are likely to get well, or at least to build up sufficient amount of blood to permit of safe operation.

Dr. Musser: I might call attention to the importance of cirrhosis of the liver simulating gastric ulcer, also the simulation of gastric ulcer by perigastric or periduodenal inflammation secondary to cholecystitis and hence the very great value of a history of typhoid fever antecedent to gastric symptoms, and particularly of the type of typhoid fever during the attack. Cases of typhoid fever going over a long period of time with an imperfect convalescence are so often due to cholecystitis which is frequently followed by gastric symptoms Therefore, while at present we are on the lookout for occurrence of cholecystitis in typhoid fever, cases of typhoid fever which occurred before our attention was called to infection of the gall-bladder must be looked into carefully to determine the character or course of the disease during the time of the typhoid infection.

Dr. Thompson: In collecting these cases great pains were taken to exclude all those of evident cirrhosis and the possibility of their being due to chronic cardiac disease and other causes. They were all cases in which the diagnosis seemed to justify that of gastric ulcer.

In regard to not finding any ulcer in operation it is quite true that one may overlook small punctate erosions, but even in these cases operation has been successful by relieving the symptoms, and surgeons have largely abandoned trying to find the ulcer and perform gastroenterostomy for the purpose of relieving the stomach from mechanical irritation, giving it rest and bringing about a better general condition.

Two years ago I had another patient operated on for gastric ulcer. She had been a miserable sufferer from gastric distress for many years, but was cured by gastroenterostomy. The surgeons have been studying this question for a long time, and it is interesting to note the impression a discussion of this topic makes upon a surgical audience, as contrasted with that made upon a medical

one. When it can be shown that in 1 case in 4½ of gastric ulcer with hematemesis death ensues without operation, the patients are entitled to at least an exploratory surgical procedure.

In two patients massive adhesions were present at the base of large ulcers, and the patients' condition did not permit of gastroenterostomy. The adhesions were liberated and both patients are well to-day, after periods of five and four years, respectively.

THE PATHOLOGIC ANATOMY OF EXOPHTHALMIC GOITER.

PRELIMINARY REPORT.

By W. G. MacCALLUM, M.D.,
ASSOCIATE PROFESSOR OF PATHOLOGY, JOHNS HOPKINS UNIVERSITY, BALTIMORE.

NOTWITHSTANDING the general agreement as to the histologic characters of goiter in Graves' disease, as described in literature, the most recent authors, A. Kocher and Reinbach, declare that there is no constant typical anatomic alteration. Nevertheless, in our series of 28 cases there has been found a lesion similar to that described by Farner with great constancy, although not always in the same degree. It is noteworthy that these cases were not derived from goiter regions. The more extreme alterations correspond exactly with those described by these various authors in the majority of their cases, but there are some in which these changes are found only in foci scattered through the gland.

Characteristic changes are to be observed in: (1) the form and size of the alveoli; (2) the character of the epithelial cells; (3) the character of the colloid; (4) the vascular supply; (5) the connective-tissue framework; (6) the lymphoid structures of the thyroid.

The alveoli vary greatly in size and form, many of them showing remarkable folding of the epithelium, so that the cavities have the appearance of sending off long diverticula. Frequently these diverticula become constricted off from the remainder and new alveoli are thus formed. Sometimes these small, new alveoli are very numerous and surround the older ones in the form of a

colony, which may be outlined by the denser stroma which surrounds the whole. This resembles almost exactly the alteration which was produced in the experiments of Dr. Halsted after the partial extirpation of the thyroid gland—that is, the condition of compensatory hypertrophy.

Changes in the epithelium consist, in general, in an alteration from the flat or cubical type to the high, cylindrical form. The cells show frequent mitotic figures, and there are abundant granules of fat in their protoplasm. The cylindrical form is characteristic, but the height of the cells varies greatly. Alteration, such as the formation of the colloid cells of Langendorff and Hürthle and the *schmelzepithel* of Hürthle, are frequently found, but it seems probable that these are degenerative changes. Langendorff's canals are not to be seen. Occasionally there occur in the walls of the alveoli very large cells, with very large vesicular nuclei, which are intercalated in the lining of cylindrical cells. There appear also intercalated cells or whole groups of cells, or even groups of alveoli lined with large irregular cells provided with deeply staining nuclei and with granular eosinophile protoplasm. These have been described by Farner and Haemig. Their significance is not clear.

The alterations in the colloid consist chiefly in its marked diminution in amount and in the ragged appearance of that which is present. The colloid in some places is homogeneous in appearance and fills at least some of the alveoli, but in many cases it is reduced to minimum and appears only as a shreddy, vacuolated, granular mass. It is usually retracted from the epithelium, being connected with it by threads which run to the lines between the epithelial cells, and there is left a thin covering of colloid over the surface of the epithelium. It is apparently easy to show by the direct application of fixing reagents to frozen sections of the thyroid that this separation from the epithelium is a retraction phenomenon, and not due to the appearance of a colorless secretion over each cell. The colloid frequently contains desquamated cells and leukocytes. Its relations to the interstitial tissue and the lymphatic and bloodvessels have been much discussed. It has been pointed out

by Quervain that it is impossible, with our present methods, to recognize colloid with certainty in the veins, that probably the hyaline material seen in the veins or in the lymphatics is largely composed of coagulated plasma, although it may contain a greater or less amount of colloid. We have found no particular excess of this hyaline material in the lymphatics in most of our cases.

The vascular supply is extraordinarily rich, the veins being especially large and distended with blood at the operation, although in the specimen as sent to the laboratory they are inconspicuous. The friability of their walls has been remarked upon by the operator. They lie embedded for the most part in the very abundant connective-tissue framework of the thyroid, which is in all cases quite definitely increased in density, considerable bands of fibrous tissue being found to run through the gland and to cause a distinct lobulation of the tissue. In this interstitial connective tissue there is found also a great deal of lymphoid tissue in the form of circumscribed, scattered, lymphoid nodules, with definite *keimcentra* and well-defined architecture. Corresponding with this increase in the lymphoid nodules there is an enlargement of the neighboring cervical lymph glands and of the thymus.

The thyroids in many cases show the presence of circumscribed prominent nodules, sometimes in considerable number, which are composed of a more homogeneous tissue, and which on section are seen to be made up of uniform, small, round alveoli, usually widely separated from one another, and embedded in a hyaline connective tissue. These are lined with plump, rather cubical epithelium, and may or may not contain colloid material. They are usually very sharply marked out from the remaining thyroid and may sometimes show an excessive number of the altered epithelial cells described above—that is, those with giant nuclei and with eosinophile protoplasm. These circumscribed nodules are found in other conditions of the thyroid and are not characteristic of exophthalmic goiter. Cysts of various sizes, usually containing a clear, greenish somewhat glutinous fluid, may also occur.

No bacteria or characteristic cell inclusions could be demonstrated by microscopic, cultural or inoculation methods.

The parathyroid glands were examined in nine cases and were found to be practically normal in all. They show in some instances a moderate atrophy of cells and induration, or increase in the interstitial connective tissue, but the alterations do not seem to be constant or sufficiently extensive to support the idea that the parathyroids have anything to do with the development of the disease known as exophthalmic goiter.

On the whole, the anatomic picture resembles most closely that produced by Dr. Halsted as a compensatory hypertrophy, and it seems probable that this may be explained by some previous injury to the gland, possibly from some foregoing infectious disease, such as influenza, etc., although a definite history of this kind cannot always be obtained. Similar changes may frequently be produced experimentally in dogs by the injection of some injurious material into the thyroid vessels, or even by the maintenance throughout a considerable time of a suppurative peritonitis, in which, apparently by the diffusion of some poisonous substance, there occurs a destruction of many of the epithelial cells of the thyroid, which later are replaced by the compensatory hypertrophy of the remaining cells. The nature of the primary injury which may produce such a change in exophthalmic goiter is, however, by no means always clear.

DISCUSSION.

Dr. Kelly: I should like to ask whether you found changes in the cervical sympathetic, and if so, what influence ablation of the cervical sympathetic would have?

Dr. MacCallum: I have had no opportunity to examine the sympathetic ganglia in these cases. In the records of microscopic examination to be found in the literature no very definite or constant lesion has been described. Undoubtedly the exophthalmos is favorably affected by excision of the sympathetic ganglion, but it seems that this is not sufficient evidence that the general condition is dependent upon a lesion in that situation.

THE NATURE AND THE LESIONS OF CIRRHOSIS OF THE LIVER, WITH SPECIAL REFERENCE TO THE REGENERATION AND REARRANGEMENT OF THE LIVER PARENCHYMA.

By A. O. J. KELLY, M.D.,
OF PHILADELPHIA.

The study of cirrhosis of the liver has been approached from several points of view, etiologic, anatomic, and clinical; but since the disorder was first described by Vesalius special interest has centered in the obvious and most conspicuous feature of the lesions—the fibrosis—so much so, indeed, that the term "cirrhosis," first employed by Laënnec to describe the yellowish (κιρρός) "hobnails," which he regarded as new-growth, has by a curious transference of meaning become almost inseparable from, with some writers practically identical with, the sclerotic process, and indeed by the ill-informed its meaning is not infrequently expanded so as to include sclerotic and fibrotic processes in other organs. As contrasted with the conspicuous fibrosis the changes in the parenchyma of the liver in cirrhosis have received comparatively scant attention. They are commonly, though of course not universally, looked upon as progressively and continuously degenerative or atrophic, usually subsidiary in importance, and secondary to, consequent upon, the changes in the interstitial tissue. It is true, however, that the so-called pseudobile-ducts, or canaliculi, present in many cases of cirrhosis, are usually nowadays looked upon as evidences of a regenerative process; that the liver cells are further capable of quite extraordinary regeneration is now well known in consequence of experimental investi-

gations and the study of the changes following acute yellow atrophy and allied processes, and such regeneration is generally recognized in the adenoma-like formations that occur under diverse circumstances; but that any noteworthy regeneration of the liver cells is a part of ordinary cirrhosis is not commonly taught.

It has long been recognized, however, that much as we have felt that we know concerning the liver and its perversions of function and alterations of structure, much more remains to be learned. Though the clinical recognition of cirrhosis of the liver may be a comparatively easy matter in many cases, the condition is not infrequently overlooked, and it constitutes a not uncommon accidental finding at the necropsy; and the divers classifications of the process (or processes) proposed by different writers—some based largely, others exclusively, upon the nature, disposition, arrangement, etc., of the fibrous tissue—and the discussions relative to what is and what is not cirrhosis (in an acceptable sense) indicate only too well that many questions pertaining to the subject still await solution. The general obscurity of many of these questions was well emphasized by Dr. Cheadle[1] in his Lumleian lectures for 1900, when he suggested the following as "among the questions awaiting an accepted and final settlement: Is atrophic cirrhosis—that is, the contracted hobnail liver—always of alcoholic origin? Is the liver small from the first, or is there an earlier stage in which it is enlarged, becoming contracted later; or is atrophic cirrhosis merely a late stage of hypertrophic cirrhosis; or is there an alcoholic cirrhosis in which the liver is hypertrophied and enlarged from first to last; or is hypertrophic cirrhosis limited to the biliary cirrhosis of Hanot and Charcot of uncertain origin; or, it is even asked, does the biliary form described by French authorities exist at all as a distinct entity? Again, is ascites limited to the atrophic form, almost unknown in the hypertrophic; while, on the other hand, is jaundice rare in atrophic cirrhosis, almost invariable in the hypertrophic form? Are the microscopic characters of monolobular cirrhosis, with

[1] Some Cirrhosis of the Liver, 1900.

hyperplasia of the bile-ducts, as described in the biliary cirrhosis of Hanot and Charcot, found only in cases that correspond to that clinical type; or are they met with in both atrophic and hypertrophic cirrhosis of alcoholic origin? The part played by alcohol, syphilis, and malaria in causation and their connection with special types of the affection; the incidence and significance of perihepatitis; the curability of ascites; the efficacy of paracentesis or its uselessness in the treatment of it; the possibility not of curing cirrhosis, but of prolonging the life of the cirrhotic patient by this or other means; the conditions under which the course of cirrhosis can be favorably influenced in this way, are other points about which there is lack of general agreement."

Although progress has been made since the time of Dr. Cheadle's lectures, which was about contemporaneous with a reviewed interest in cirrhosis of the liver, much still awaits elucidation. The difficulty in the past has been due largely to the points of view from which the phenomena of cirrhosis have been studied, to the fact that the late lesions are those that necessarily have been most investigated, to the bases of classifications commonly adopted, and to the comparative inelasticity of the descriptive terms employed, all of which are excellently intimated by Dr. Cheadle in his queries. The recent studies and several communications of Kretz,[1] however, throw considerable light upon the nature of cirrhosis, and the still more recent communications by MacCallum[2] and Boström,[3] as well as the results of some experimental work, notably recently by Pearce,[4] lend confirmation to his views. My own work, which in some particulars is merely confirmatory of the already published work of Kretz and of MacCallum, is based upon a study of the thirty cases of cirrhosis, and of many other cases of disease of the liver, that have come to

[1] Ueber Lebercirrhose, Wien. klin. Woch., 1900, vol. xiii. p. 271; Lubarsch und Ostertag's Ergebnisse der allg. Path. und path. Anat., 1904, vol. viii. p. 473 (bericht über das Jahr., 1902); Verhandl. der deut. path. Gesellschaft, 1904, vol. viii. p. 54; International Clinics, 1905, 15th series, vol. iii. p. 289.

[2] Regenerative Changes in Cirrhosis of the Liver, Jour. Amer. Med. Association, 1904, vol. xliii. p. 649.

[3] Lebercirrhose, Deut. med. Woch., 1905. vol. xxxi. p. 167.

[4] A paper on Experimental Cirrhosis of the Liver, read at the meeting of the American Association of Pathologists and Bacteriologists in Chicago, April, 1905, and to be published in the Journal of Experimental Medicine.

necropsy at the German Hospital, Philadelphia, during the last eight years; certain clinical data of patients treated in the German Hospital during the last fifteen years, in whom a diagnosis of cirrhosis of the liver was made—for permission to use which I am much indebted to Dr. James C. Wilson, physician-in-chief to the German Hospital; several cases of cirrhosis observed on Dr. Musser's service in the University Hospital, for permission to utilize which I am much indebted to Dr. Musser; several cases observed on my own service at St. Agnes' Hospital; many of Professor Kretz's preparations; and other pieces of tissue from unusual cases, for which I am indebted to several friends, notably Dr. W. F. Hamilton, of Montreal, Dr. Allen J. Smith, of Philadelphia, Dr. W. M. L. Coplin, of Philadelphia (spontaneous cirrhosis in dogs), etc. I shall consider (1) the structure of the liver in so far as it has a bearing upon the changes in cirrhosis; (2) the changes in the parenchyma of the liver in cirrhosis; (3) the changes in the connective tissue in cirrhosis; and (4) the permissible deductions with regard to the nature of cirrhosis that may be drawn from the foregoing.

The Structure of the Normal Liver. Although it is largely supererogatory at this day to discuss the structure of the normal liver, a clear conception of the cirrhotic process is best attained by bearing in mind that, as recognized years ago by Hyrtl[1] and recently especially emphasized by Kretz, the liver is not made up of acini in an acceptable sense. While the physiologic unit of the liver is that collection of cells drained by a radicle of the bile-duct, this unit is scarcely delimitable anatomically, although Sabourin[2] has made an attempt to do so; nor are the so-called acini, or lobules, cross-sections of which surrounded by connective tissues form such a conspicuous feature of microscopic sections, of such simple structure as at first sight appears. Study of the liver in serial sections and its reconstruction show that the liver parenchyma does not form isolated acini, or lobules, everywhere surrounded by connective tissue, but that what

[1] Lehrbuch der Anatomie des Menschen, 1873, 12te Aufl., p. 639.

[2] Étude compare du foie de l'homme et du foie du cochon, Revue de méd., 1901, vol. xxi. p. 384.

appear to be acini are merely cross-sections of liver cells arranged as a mantle about the numerous dendritic ramifications of the hepatic vein, and that this mantle is nowhere discontinuous, forming, on the contrary, a continuous whole, everywhere connected, particularly at the points of junction of the sublobular, lobular, and lobar veins. The intimate relationship that the liver cells structurally bear to the hepatic vein is further shown by the radial disposition of the cells about the branches of this vein, the so-called central veins. Toward the periphery of the liver anastomoses may sometimes be found between branches of the hepatic vein, and in some of the lobules one sometimes encounters rather large branches of the central vein, about which the liver cells are arranged radially. Thus we find that the liver consists not of acini, but of mantles of cells arranged radially about the arborescent ramifications of the hepatic vein, and that cross-sections of so-called acini are really cross-sections of cell mantles, which, however, may also be cut longitudinally or tangentially.

Sabourin has attempted to modify the current conception of the so-called acini in that he looks upon the center of the acinus, or lobule (according to his conception), as the portobiliary nodule, the point of breaking up of a radicle of the portal vein and of the confluence of the biliary capillaries to form a biliary radicle; the extent of the acinus, as the area of distribution of a portal radicle with its accompanying hepatic artery, bile-duct, and related liver cells; and the periphery of the acinus as the so-called rectilinear veins, small intralobular veins, formed by fusion of capillaries that empty at right angles into the central veins. In the swine these rectilinear veins are accompanied by connective tissue from the periportal connective tissue to the central veins, and Sabourin believes that the counterpart of this exists in the human subject. It is to be found especially in cases of long-standing chronic congestion. This conception of the architecture of the liver is of some interest, since it serves to correlate the anatomic with the physiologic unit, but as far as we are concerned at present it merely substitutes the portal for the hepatic vein, since in both cases the hepatic cells form a continuous mantle—of the branches

of the portal vein in the one case, of the branches of the hepatic vein in the other case.

Pervading and filling the spaces left between the arborescent ramifications of the hepatic vein with its cell mantles are the radicles of the portal vein, accompanied by the hepatic artery and the bile-ducts, all supported by connective tissue (the capsule of Glisson), sparse in some places, more abundant in others; but such is the arrangement of the intertwinings of the "portal tree" and the "hepatic tree" that the finest ramifications of the one are everywhere separated from those of the other by a collection (mantle) of liver cells.

As distinguished from most other organs the liver has two sources of blood supply—the portal vein and the hepatic artery —which commingling form a plexiform capillary network, in the meshes of which the liver cells are arranged. Ultimately the capillaries unite again to form the radicles of the hepatic vein—the rectilinear veins of Sabourin, which empty into the so-called central veins. The circulation within the liver, which is not only interesting in itself but of much importance in connection with certain features of cirrhosis, has recently been studied attentively by Opie.[1] It has long been known, and Opie directs renewed attention to the fact that one of the important characteristics of the liver is its susceptibility to variations in blood pressure, saying: "The portal vein, hepatic artery, and hepatic vein are in such free communication that the entire lobule can be injected from any one of these vessels. Hence, artificial injections do not define the intralobular distribution of the portal and arterial blood, for doubtless differences of venous and arterial pressures have a part in determining peculiarities of the circulation within the lobule." Opie's experimental studies led him to the conclusion "that both the hepatic artery and portal vein pour their blood into the periphery of the lobule, and here the influence of the arterial blood pressure is most strongly felt. When foreign material reaches the liver by the portal vein it is washed from the peripheral zone by the arterial blood, and tends to be deposited in a

[1] Zonal Necrosis of the Liver, Jour. Med. Research, 1904, vol. xii. p. 147.

middle zone, where the influence of the opposing circulation is less strongly felt. Hence, it is not improbable that toxic substances capable of causing necrosis of the hepatic cells, brought to the liver by the portal vein, might first exert their effect upon cells within a midlobular zone. The periphery of the lobule, moreover, is supplied with arterial blood, and is perhaps for this reason less susceptible to injurious agencies."

Changes in the Parenchyma of the Liver. If we examine attentively the parenchyma of the liver in a moderately advanced or well-advanced case of cirrhosis certain noteworthy deviations from the normal become apparent: (*a*) Changes in the size of the lobules; (*b*) changes in the shape and configuration of the lobules; (*c*) changes in the arrangement of the liver cells; (*d*) degenerative or atrophic and hyperplastic changes in the liver cells; and (*e*) changes in the vascular arrangement and supply.

Changes in the Size of the Lobules. One of the patent and noteworthy features of the lesions of cirrhosis is the marked variation in size of the "granules" or "hobnails," which not only vary considerably in size in different cases, but also in the same case in different parts of the liver, some being notably smaller, others notably larger than the lobules of the normal liver. Long identified as the analogue of the normal liver lobule, it is now well known that many of them are made up of several lobules or of the remains of several lobules; but it is important to bear in mind that some of them are really single lobules, departed, however, somewhat from the normal. The question of the size of these lobules has recently been studied attentively by Kretz, MacCallum, etc. Kretz, pointing out that the normal lobules are roundish-polygonal in shape, with their long axis in the direction of the central vein, states (as is well known) that their greatest diameter is usually a little more than 1.5 mm., and may reach 2.5 mm., whereas the short diameter is about 1 mm. and that in cirrhosis these figures are surpassed, some lobules being much larger and other collections of cells much smaller. MacCallum found that while the average radius of a lobule (that is, the thickness of the mantle of cells about the central vein) in a number of normal livers is about 0.66 mm., in

advanced cirrhosis lobules are encountered that measure from central vein to periphery 1 mm. or more, the small diameter, therefore, being more than 2 mm. My own observations amply confirm the truth of these statements. I have not, however, been able to confirm Brissaud and Dopter's[1] statement that the lobules of the right lobe are considerably larger than those of the left.

Changes in the Shape of the Lobules. With the central vein as a point of departure, we find that, as already stated, the lobules are roundish-polygonal in shape, their long axis being in the direction of the central vein and their cross-sections roughly rounded, and that the veins are in reality central—that is, surrounded on all sides by an even thickness or mantle of cells. In diagonal or tangential sections of lobules this is not so apparent, and the picture is altered where several lobules join or where the liver cells vary somewhat their course to form the continuous mantle, especially about the junctions of sublobular and lobular veins. In cirrhosis there is a notable departure from this shape and configuration. Many of the lobules are no longer rounded, but quite irregular in transverse section. Many of the cell mantles no longer surround the central veins equally on all sides, but very unequally, so that many central veins are situated eccentrically in a more or less misshapen lobule. Many so-called lobules have no central veins at all (and are not tangential sections of otherwise normally arranged lobules). Certain lobules (or so-called lobules, usually remains of several) have two, three, four or more central veins, and often the central vein may be seen in the adjacent interlobular connective tissue. Thus, we ascertain that the mantle of cells covering a central vein varies much in thickness in different regions (transverse planes), sometimes exposing, sometimes covering the vein to a greater or less extent; and that, though isolated collections of liver cells—that is, collections devoid of central veins—do occur, some supposedly isolated collections are merely sections of more or less irregularly proliferating dendritic branches of what may be called the parent stem or mantle covering a single central vein.

[1] Note sur les differences de volume des lobules hepatiques du foie humain, Gaz., hebd. de med., 1902, vol. xlix. p. 661.

Changes in the Arrangement of the Liver Cells. A conspicuous feature of the normal liver lobule is the radial arrangement of the liver cells about the central vein. In cirrhosis, although this arrangement is preserved to some extent, in many places its partial or complete absence is noteworthy. The architecture of the lobule has become altered so that the cells are arranged irregularly, in parallel rows, etc. This rearrangement of the liver cells is quite as well marked in many of the lobules that have a central vein as in those collections of cells entirely devoid of central veins.

Degenerative or Atrophic and Hyperplastic Changes in the Liver Cells. The degenerative and atrophic changes in the liver cells in cirrhosis—simple atrophy, parenchymatous degeneration, fatty degeneration, fatty infiltration, pigmentary infiltration, etc.—are a part of common knowledge, and for the moment need not be further discussed. It is important, however, with a view to the correct interpretation of the lesions, to bear in mind that many cells at the periphery of lobules (or so-called "hobnails") in immediate contiguity to wide bands of connective tissue are by no means atrophic, even in fairly well-advanced cases; on the contrary, it is really noteworthy that whereas *a priori*, in conformity with prevailing opinions, compression atrophy of these cells should be expected, and is indeed often commented upon, the cells that should exhibit this alteration most markedly—that is, those at the periphery of the lobule—often present an unusually plump and healthy appearance, and cannot therefore have been unduly compressed.

Special attention, however, should be directed to the evidences of hyperplasia of the liver cells that are readily found in almost every cirrhotic liver, even in far-advanced cases. Mitoses, it is true, are rarely encountered in advanced cases—largely in consequence of the nature of the process, the advanced stage at which the examination is generally undertaken, and the length of time after death that the liver is obtained, time sufficient for the completion of any mitoses present at death. That many of the liver cells, however, are newly formed is quite apparent from their large, clear and plump appearance, their rounded (rather than

polygonal) outline, the presence of two or more nuclei, and the absence of fat and of pigment from their protoplasm. And what is especially noteworthy is that these cells, sometimes small collections of them, are situated amidst other liver cells, normal in size and outline, provided with only a single nucleus each (though sometimes with two nuclei, which is quite normal), and the protoplasm of which is normally pigmented and contains fat. These newly formed cells are usually found at the periphery of a lobule. Sometimes they make up a larger or smaller sector of a lobule; sometimes they seem to have compressed the older cells of their immediate vicinity; and sometimes small collections of them are found completely surrounded by wide bands of connective tissue, where by their generally plump and healthy appearance they convict the connective tissue of exerting less constrictive force than they themselves expansive force. The sector of a lobule sometimes made up of these cells serves, in some cases, to restore more or less completely the normal outline of the lobule—that is, of the mantle of cells covering a central vein—in which event, a part of the mantle of cells consists of such newly formed cells arranged irregularly and a part of older cells arranged radially. In other cases this cellular hyperplasia has occurred in such a manner that the central vein is more or less exposed on one side and on the other covered with a mantle of cells often twice or thrice the normal thickness.

In acute and subacute, or what may be called recurring, cases mitoses are occasionally encountered (doubtless they would be more frequently encountered were our methods of investigation better thereto adapted), and necrotic and hyperplastic changes may be found side by side in the one lobule.

A characteristic feature of almost all cases of cirrhosis, more conspicuous, however, in some cases than in others, is the bile-ducts or so-called pseudobiliary canaliculi, the nature and origin of which has for a long time occasioned much discussion. Doubtless the great increase of these structures in cirrhosis, as contrasted with the normal liver, is relative only and due in part, but only in small part, to mutual approximation of already existing bile-ducts occurring in consequence of loss of the liver tissue; but

that most of them are newly formed is generally conceded and is quite apparent from their excessive number and the evidences of active proliferation (mitosis) that they commonly exhibit. Their origin has not been determined definitely for all cases. Dispensing for the time being with a detailed discussion of the question, it seems quite certain that some, at least, of them result from proliferation of previously existing bile-ducts; on the other hand, since they are found in a wide variety of disorders, such as all forms of cirrhosis, acute yellow atrophy, in the neighborhood of hydatid cysts, tubercles, gummas, etc.; in other words, in diseases alike only in that they destroy liver tissue; since they differ from normal bile-ducts in the absence or relative paucity of encircling elastic tissue; since they have been found by Ackermann and others to be directly continuous with liver cells; and since in cases in which the liver cells have been much destroyed they are found in large numbers in what may be interpreted as the remains of the skeleton of the lobule, we are quite warranted in the opinion that they may result from proliferation of the liver cells themselves, constituting in this event a reversion to a less highly specialized type of structure. The important fact only that I wish to point out in this connection is the histogenetic equivalence of the liver cells and the epithelium of the bile-ducts, and the fact that proliferative changes of the liver parenchyma is a conspicuous feature of common cirrhosis.

Changes in the Vascular Arrangement and Supply. Reference has already been made to the fact that the central veins are situated eccentrically in certain more or less distorted and rearranged lobules, that they may be found at the edge of certain lobules or remains of lobules, and even in the interlobular connective tissue, and that certain islets of liver tissue are totally devoid of central veins. Another noteworthy feature is that the central veins appear to have diminished in number in the liver as a whole. Corresponding to the smaller size of many of the cirrhotic livers and the associated loss of the liver parenchyma, the central veins in certain regions sometimes exhibit a mutual approximation, which, however, varies much in different livers

and in the same liver in different places. In some regions where considerable hepatic-cell hyperplasia has occurred they are often quite widely separated; but were the central veins not diminished in number in the liver as a whole we should expect to find in a small so-called atrophic cirrhotic liver a relative increase in the number of central veins in a given square surface as compared with a square surface of similar size in a normal liver—which, however, is not the case. The absolute lessening of the number of central veins becomes further evident when we recall the many islets of liver tissue (likely at first sight to be interpreted as more or less distorted lobules) entirely devoid of central veins.

Confirming the view that a number of the central veins have disappeared we may sometimes find in sections happily cut through the desired plane bulbous and distorted side branches of the sublobular and lobular veins. Furthermore, Kretz, who has studied attentively the circulation in the cirrhotic liver, seems conclusively to have proved by means of injected and macerated preparations that the finer ramifications of the hepatic vein are fewer than in the normal liver, that the sublobular and lobular branches are more tortuous and in some places larger and thicker, and that they have attached to them bulbous and distorted side branches, representing, according to him, the atrophic remains of central, sublobular and lobular veins persisting after the disappearance of the related parenchyma.

Apropos of the circulation in cirrhosis Kretz states: "If in ordinary atrophic cirrhosis an injection is made from the portal vein a small part of the hepatic tissue is, as a rule, so easily permeated that the injection mass passes over into the hepatic vein at a time when a very considerable part of the parenchyma is still uninjected; more particularly after such injection experiments the large turgescent islets of tissue and the small areas devoid of hepatic veins . . . remain unaffected. By injecting the hepatic artery, always decidedly enlarged in these cases, these very areas are most easily injected. They may also be partly injected from the portal vein if an injection mass, which passes with difficulty, is employed. Based upon these observations the circulation in the diseased liver must be depicted as

follows: a small part of the portal blood passes through the remnants of the old acinous channels into the hepatic veins; this passage forms an internal portocaval anastomosis supplementing the external; to the remaining branches of the portal vein more than the normal amount of arterial blood is furnished; this on the one hand supplies the granular areas of the parenchyma devoid of hepatic veins, and on the other the hypertrophic remains of acinous tissue. This excess of blood passes under increased pressure through the remainder of the capillaries, narrowed by atrophy of the acini and lengthened by hypertrophy of the liver tissue. The lengthening and narrowing of the capillary vessels and the excess of arterial blood are the true causes of the increase of portal pressure, as is shown by the occurrence of ascites in subacute atrophy of the liver with regeneration, but without contracting connective tissue."

Miura[1] also has made some interesting observations on the changes in the vascular arrangement that occurs in cirrhosis. Pointing out that many of the portal radicles (as is well known) gradually become obliterated, he describes the development, within more or less well-preserved lobules, of communicating vascular twigs directly uniting the portal veins with the central veins. He terms these internal collateral branches, in contradistinction to the external collaterals (those outside the liver); probably they are not diverse from or at least originate from the rectilinear veins of Sabourin. These internal collateral branches, together with their ramifications and the associated portal and central veins, sometimes become provided with connective tissue and serve to subdivide the lobule—in which event the central veins, situated where trabeculæ of such connective tissue join, are likely to be mistaken for portal veins. Usually, however, they may be distinguished by their comparative paucity of elastic tissue, as contrasted with the portal veins. It is scarcely necessary to discuss in detail the well-known changes in the portal vein itself—its increase in thickness and tortuosity, and the obliteration of many of its radicles, especially in advanced cases.

[1] Beiträge zur Pathologie der Lebercirrhose, Mittheilungen aus der Medicinischen Facultät der Kaiserlich-Japanischen Universität zu Tokio, 1900, vol. iv. p. 49.

Changes in the Connective Tissue. A study of the connective tissue in almost any well-marked cirrhotic ("coarsely granular") liver shows that it is made up of several sorts of tissue: (1) Some of it is unquestionably newly formed; of this there is no doubt, the debatable point being as to its nature and genesis; (2) some of it is the tissue originally between the lobules—the connective tissue of Glisson's capsule; and (3) some of it is the collapsed and otherwise altered reticulum of certain liver lobules, the cells of which have disappeared, evidently degenerated by some influence and subsequently removed.

As regards the newly formed tissue, its nature and distribution have been studied by a large number of investigators, and little that is new can be added to what is common knowledge. It has been demonstrated by divers methods of investigation, including the use of Weigert's elastica stain, Mallory's connective-tissue and reticulum stain, digestion with pancreatin, etc., that the normal liver contains three kinds of connective tissue: (1) White fibrous tissue, present in the liver capsule and in large amount in the interlobular spaces; (2) elastic tissue, found chiefly about the bloodvessels, to a less extent about the bile-ducts and in the liver capsule, and to a very slight extent in and about the walls of the central veins; and (3) reticulum; according to Mall[1] "a great share of the tissue accompanying the interlobular vessels and all that about the intralobular is reticulated. The peritoneal surface may be viewed as a thickening of the reticulum intermixed with some white fibers."

Whereas formerly the fibrosis of cirrhosis was generally thought to consist almost if not quite exclusively of white fibrous tissue, the studies of Hohenemser,[2] Melnikow-Raswedenko,[3] Flexner,[4] McIntyre,[5] Oliver[6] and others have shown us, and anyone can

[1] Reticulated Tissue and its Relation to the Connective-tissue Fibrils, Johns Hopkins Hospital Reports, 1896, vol. i. p. 171.

[2] Ueber das Vorkommen von elastischen Fassern bei cirrhotischen Processen der Leber und Niere, Virchow's Archiv, 1892, vol. cxl. p. 192.

[3] Histologische Untersuchungen über das elastische Gewebe in normalen und pathologisch veränderten Organen, Ziegler's Beiträge, 1899, vol. xxvi. p. 546.

[4] The Nature and Distribution of the New Tissue in Cirrhosis of the Liver, University Medical Magazine, 1900–1, vol. xiii. p. 613.

[5] Some Points in the Formation of Connective Tissue in the Liver, Glasgow Medical Journal, 1901, vol. lv. pp. 341, 415.

[6] Elastic Tissue in Cirrhosis of the Liver, Transactions of the Chicago Pathological Society, 1901–3, vol. v. p. 96.

readily demonstrate, that in reality it consists of all the connective tissues of the normal liver—pathologically altered, it is true. The most conspicuous change is the great increase in the elastic tissue —probably more or less intimately related to the great increase in the capillaries derived from arterioles; this elastic tissue not only makes up a large part of the fibrous bands between the lobules, but it is also found to some extent within the lobules, and occasionally a very small amount of it is found about or in the immediate neighborhood of the central veins. A not inconsiderable part of the fibrosis is made up of reticulum—not only the reticulum normally between the lobules, but also the intralobular reticulum—that remaining after the liver cells have degenerated and been removed. This collapsing intralobular reticulum may be quite readily distinguished in tolerably early cases; later, however, when it has become a part of the interlobular fibrosis it can scarcely be recognized as a distinct entity. I believe that Flexner is quite correct in the opinion that the changes in the reticulum in cirrhosis constitute an hypertrophy rather than an hyperplasia of the fibrils.

The distribution of the connective tissue in cirrhosis has long been the subject of much and more or less fruitless discussion; and the many classifications based thereupon have not tended to clarify any of the obscurity connected with the subject. Multilobular, monolobular, and pericellular (as well as certain more or less synonymous terms, such as annular, circumlobular, unilobular, interlobular, extralobular, intralobular, perilobular, intercellular, etc.) are in common use, and are said to be descriptive of special types of the disease. Without entering upon a detailed discussion of the question at the present time, I may point out that while one or the other of these varieties of distribution of connective tissue may appear to predominate in certain cirrhotic livers, all varieties are much more likely to be encountered in the one liver; and while so-called "hypertrophic" or biliary cirrhosis, as contrasted with so-called "atrophic" cirrhosis, is usually characterized by less interlobular fibrosis and an earlier and a finer intralobular fibrosis, it is frequently impossible from a mere microscopic inspection of a section of a cirrhotic liver to state to

which type of the disease it belongs. Assuredly in the advanced stages the lesions tend to become very much alike. The difficulty is overcome by some writers who postulate so-called "mixed" cases.

The Nature of Cirrhosis. Endeavoring to interpret the foregoing lesions we find that the most noteworthy feature is the complete rearrangement of the architecture of the liver parenchyma. In consequence of some cause or causes larger or smaller portions of numerous liver lobules have been destroyed, many liver lobules have been destroyed entirely—whence the necrotic changes and the skeleton of the reticulum remaining after removal of the cells that are apparent in the early stages, and the eccentric and otherwise irregular situation of many central veins (the variations in size and outline of the cell mantles) and the complete disappearance of other central veins that are apparent in the advanced stages of the disease. Furthermore, evidences of regeneration and hyperplasia of the liver cells are quite apparent—in the general appearance of many of the cells themselves, in their irregular arrangement, in parallel rows, etc. (as contrasted with the normal radial arrangement), in the large hyperplastic lobular (so-called adenomatous) masses, in the irregular dendritic ramifications of liver cells with a peculiar vascularization and entirely devoid of central veins, in the pseudobile canaliculi, etc. Although evidences of secondary atrophy of the liver cells are by no means wanting, especially in advanced cases, the peripheral cells of many of the lobules in early cases, but often also in well-advanced cases, exhibit no evidences of compression atrophy whatever—being plump and well formed and manifesting therefore more expansive force than the surrounding connective tissue constricting force; some of the small islets of liver tissue containing central veins, since their peripheral cells exhibit no evidences of compression, must have resulted from degeneration and subsequent regeneration of the liver tissue; and some of the small islets devoid of central veins, since they exhibit no evidence of peripheral compression nor of capillary stasis, cannot have resulted from sequestration of a part of a lobule by invading connective tissue, but must represent regenerated liver

tissue. The parenchyma of the liver in cirrhosis, then, consists not only of remnants of the original parenchyma, but also and in large part of regenerated liver tissue that differs from normal liver tissue in that it does not reproduce its typical architecture nor its relation to the bloodvessels—the capillaries and the central veins.

That the liver is capable of this really remarkable regeneration has been amply proved—especially by Ponfick,[1] von Podwyssozki,[2] von Meister,[3] and others, particularly Pearce,[4] recently, who have studied regeneration of the liver experimentally; by Marchand,[5] Meder,[6] Stroebe,[7] Barbacci,[8] Mertens,[9] MacCallum,[10] and others who have studied the regenerative lesions following acute yellow atrophy; by the many observers (a good collective list of whom is given by Barbacci) who have studied the adenoma formations in the liver; and by Kretz,[11] Greco,[12] MacCallum,[13] and Böstrom,[14] who have studied the regenerative changes in cirrhosis.

The present is not the time to discuss these regenerative changes in detail, and I must content myself with pointing out that the changes found in cirrhosis when compared with those

[1] Experimentelle Beiträge zur Pathologie der Leber, Virchow's Archiv, 1889, vol. cxviii. p. 209; 1890, vol. cxix. p. 193; 1895, vol. cxxxviii. (sup. Heft) p. 81.

[2] Experimentelle Untersuchungen über die Regeneration der Drusengewebe, I Theil, Lebergewebe, Ziegler's Beiträge, 1886, vol. i. p. 259.

[3] Ueber die Regeneration der Leberdrüse nach Entfernung ganzer Lappen, Centralblatt f. allg. Pathologie und path. Anatomie, 1891, vol. ii. p. 961.

[4] The unpublished paper on Experimental Cirrhosis of the Liver previously referred to.

[5] Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasia, Ziegler's Beiträge, 1895, vol. xvii. p. 206.

[6] Ueber acute Leberatrophie mit besonderer Berücksichtigung der dabei beobachteten Regenerationserscheinungen, Ziegler's Beiträge, 1895, vol. xvii. p. 143.

[7] Zur Kenntniss der sogenannten acuten Leberatrophie, Ziegler's Beiträge, 1897, vol. xxi. p. 379.

[8] Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasia, Ziegler's Beiträge, 1901, vol. xxx. p. 49.

[9] Lesions anatomiques du foie du lapin au cours de l'intoxication chronique par le chloroform et par l'alcohol, Archives international du pharmacodynamie, vol. ii. p. 127 (quoted by Kretz).

[10] Regenerative Changes in the Liver after Acute Yellow Atrophy, Johns Hopkins Hospital Reports, 1903, vol. x. p. 375.

[11] Loc. cit.

[12] Ueber Reproduction der Leber bei Cirrhose, Centralblatt f. allg. Pathologie und path. Anatomie, 1898, vol. ix. p. 371 (abstracted from La Riforma Medica, 1897, vol. iii.).

[13] Regenerative Changes in Cirrhosis of the Liver, Jour. Amer. Med. Assoc., 1904, vol. xliii. p. 649.

[14] Loc. cit.

found, for instance, by Ponfick in experimental hypertrophy of the liver, are found to be identical; that is, for a short time after removal of a portion of the liver mitoses are quite abundant, but later the new-formed liver tissue partakes of the characters of the liver cells in cirrhosis that I have already mentioned—large, clear, plump cells with rounded outline, containing two or more nuclei, devoid of fat and pigment, and occurring often in the midst of other cells differing in no way from the common liver cells (smaller, usually polygonal, with a single nucleus, normally pigmented and containing fat, and sometimes even compressed by the newly formed cells).

The nature of the fibrosis in cirrhosis has long engaged the attention of pathologists; whether it is an inflammatory or a replacement fibrosis is still a matter of discussion. Although the question may not be definitely decided offhand, there are many facts which suggest that the prevailing opinion that the cause of cirrhosis, whatever it may be, engenders a primary overgrowth of connective tissue is not correct. I have just mentioned certain facts that show that the lesions of the parenchyma in cirrhosis cannot with reason be regarded as secondary to (dependent upon) changes in the connective tissue—since no connective tissue change with which we are acquainted is capable of causing the noteworthy rearrangement of the architecture of the liver so characteristic of cirrhosis, and as a matter of fact the liver parenchyma, even in many advanced cases, exhibits a notable absence of compression atrophy—a change that is so conspicuous, for instance, about a growing metastatic carcinomatous nodule in the liver.

As is well known, there is a disposition among pathologists during recent years to separate from the purely inflammatory conditions certain fibroses of which the fibroid heart, the chronic granular and arteriosclerotic kidney, certain so-called senile fibroses, sclerosis of the nervous system, and cirrhosis of the liver and conspicuous examples. The scleroses of the nervous system are now almost universally believed to be examples of replacement fibrosis—hypertrophy and hyperplasia of the neuroglia to replace lost or destroyed nervous elements; in the fibroid heart, in many if not all cases, the cardiac muscle has degenerated in conse-

quence of deficient nutritive supply or other cause, and becomes replaced by fibroid connective tissue; and other examples of such replacement fibrosis are found in pseudohypertrophic muscular paralysis and the atrophy of certain fetal structures at or shortly after birth. There is considerable evidence that the fibrosis of cirrhosis also is of the same nature—at least in part. The lesions of acute inflammation are scarcely if ever encountered (in view of the chronicity of the process this excites little comment), and when found they are not infrequently due to some complication; the changes in the reticulum are, as suggested by Flexner, hypertrophic rather than hyperplastic, and may be explained by recourse to Ribbert's theory of tissue tension; the new tissue, as a rule, is unusually rich in intercellular substance, as contrasted with cells; and many of the cells are doubtless only evidences of the effort on the part of nature to remove effete matter—necrotic liver cells. On the other hand, we cannot deny that a poison or other etiologic factor capable of causing necrosis of the liver cells may also be capable of setting up inflammatory phenomena in the interstitial tissue, although the parenchymatous cells are probably more susceptible to injurious influences; and in other cases the necrotic liver cells, being foreign bodies, act as a source of irritation, whence it is likely that if the fibrosis is largely a replacement fibrosis in some cases, in other cases it is both a replacement and inflammatory fibrosis.

As regards the nature of cirrhosis, then, I may say with Kretz that it is a chronic focal or localized, recrudescing degeneration and partial destruction of the liver parenchyma attended by marked regenerative phenomena on the part of the liver cells leading to complete transformation of the architecture of the liver and followed by fibrosis. It is not a primary interstitial hepatitis, the changes in the connective tissue being altogether secondary in importance and sequence, probably in large part a replacement fibrosis to fill up potential lacunæ left by degenerated liver cells, and probably in some cases at least partly inflammatory. In consequence of the activity of some poison or other etiologic factor larger or smaller areas of the liver tissue, that is, of the cell mantles about the central veins, become

necrotic and are removed—whereby the central veins become more or less uncovered, thus on cross-section appearing eccentrically situated in more or less misshapen lobules; in some cases in which the destruction of liver cells has been through the entire radius of the cell mantle the central vein may be entirely exposed and may even be found in the interlobular connective tissue—in which event it is very likely to be mistaken for a branch of the portal vein. The cells destroyed are those about the periphery of the lobules—in the area of portal distribution, conforming to the fact that the etiologic factor (poison) is usually carried by the portal vein. In case the poison is carried by the hepatic artery (as seems likely in some general infections) the lesions may be somewhat diverse, in the beginning of the process at least; and it is by no means improbable (though this still awaits proof) that the differences between the common or Laënnec's cirrhosis and so-called hypertrophic cirrhosis are in part at least dependent upon the source (portal vein or hepatic artery), in part also upon the nature, of the provoking cause. Following the primary destruction of certain liver cells, the intact cells, exhibiting a remarkable regenerative capacity, attempt to replace the lost cells and sometimes succeed in restoring more or less completely the volume of the cell mantles. The cells that regenerate are those in the immediate vicinity of those that have become necrotic; that is, in the ordinary case in which the destruction is not widespread, cells toward or at the periphery of the lobule—which thus are not only most exposed to the deleterious influence of poisons carried by the circulation, but in consequence of being better supplied by arterial blood are also better adapted for repair. I am rather inclined to believe, in view of Opie's researches on the circulation within the lobules, that the primary destructive action may be exerted, at least sometimes, in the so-called midlobular zone—at all events, not immediately at the periphery; that the peripheral cells, being better supplied with arterial blood, survive when others nearer the centre of the lobule succumb; and that these peripheral cells also serve as a focus of regeneration, though, of course, the cells nearer the centre of the lobule also regenerate. I am somewhat confirmed in this opinion by the characteristics

and disposition of many of the pseudobiliary canaliculi which are often most numerous in the skeleton of those lobules that have been much destroyed, and seemingly grow from the periphery into the lobule, in a manner quite analogous to Ponfick's and others' descriptions of their growth into granulation tissue after destruction of the liver cells. As is now generally conceded, these pseudobiliary canaliculi sometimes grow from pre-existing bile-ducts, but as I have already pointed out and as is well known, they also develop from liver cells, which in this respect are histogenetically equivalent with the epithelium of the bile-ducts. It is also not unlikely that some of the surviving peripheral cells by proliferation give rise to certain of the hyperplastic islets of liver tissue devoid of central veins.

The continuing activity of the etiologic factor leads to a continuous or recrudescing death of certain old as well as newly formed liver cells, which in turn is followed by renewed regeneration. This continuous degeneration and regeneration ultimately lead to complete transformation of the architecture of the liver: certain lobules are entirely destroyed, others are partly or completely rearranged, some are markedly hyperplastic though tolerably well arranged, some show dendritic and other irregular proliferation, new islets of liver tissue entirely devoid of central veins appear, and what is especially important new circulatory conditions—capillary and venous—arise.

Concurrent with the degeneration of the liver cells the framework of the lobules collapses and participates in the formation of the fibrosis. This fibrosis, formed as previously described, ultimately contracts, and on the one hand causes atrophic changes in the liver cells, and on the other obstruction and obliteration of some of the interlobular and intralobular branches of the portal vein; this latter, though it contributes to, is not the sole cause of, the ascites—other important factors being the aforementioned new circulatory conditions, especially certain noteworthy changes in the hepatic arterial supply (that need not be further discussed here). Ultimately the potentiality for regeneration possessed by the liver cells and manifested to a remarkable degree, not only in the early but also in the late stages, gradually lessens and is finally

lost, the general functional capacity of the liver cells being meanwhile compromised by the contracting connective tissue; the degenerative changes predominate over the regenerative and the patient soon dies, if he has not succumbed earlier to an accidental infection to which his depressed vitality renders him especially susceptible.

The conspicuous change in the cirrhotic liver at necropsy, then, is the evidences of regeneration of the liver parenchyma; the evidences of degeneration, though sufficiently manifest in early cases, in advanced cases are commonly past and represented only by the newly formed and rearranged liver tissue and the fibrosis; and the liver as a whole may be said to represent its, for a time at least, partially successful efforts to compensate the consequences of the continuous or intermittent activity of the etiologic factor—usually a poison, though in some cases possibly a substance causing thrombosis of the portal or hepatic artery radicles.

The idea of the primary change in cirrhosis being in the parenchymatous tissue is by no means new. It was entertained many years ago by Frerichs,[1] Ackermann,[2] Orth[3] and others, and, indeed, Laënnec,[4] who originated the term, was not altogether wrong when he looked upon the "granules" as new-growth, though they can scarcely be considered neoplasms, as he believed; the likelihood or possibility of the primary changes being in the parenchymatous tissue is conceded by Ziegler,[5] Rolleston[6] and others; its probability is suggested by the results of the work of the many observers who have studied the subject experimentally; it has recently been insisted upon by Kretz, Böstrom, and MacCallum; and it seems rather conclusively to have been proved recently by Pearce—who experimenting with hæmagglutinative serums produced primary focal or widespread necrosis

[1] Klinik der Leberkrankheiten, 1861, vol. ii. p. 19, and Atlas. (Also translation by the New Sydenham Society.)

[2] Ueber hypertrophische und atrophische Lebercirrhose, Virchow's Archiv, 1880, vol. lxxx. p. 396; Die Histogenese und Histologie der Lebercirrhose, Virchow's Archiv, 1889, vol. cxv. p. 216.

[3] Lehrbuch der spec. path. Anatomie, 1887, vol. i. p. 939.

[4] Traite de l'Auscultation médicale, 1819, vol. i. p. 368.

[5] Lehrbuch der allg. Pathologie und path. Anatomie, 1898, 9te Aufl., vol. ii. p. 591.

[6] Diseases of the Liver, Gall-bladder, and Bile-ducts, 1905, p. 196.

(depending upon the dose of the serum employed) with consecutive repair on the part of the liver cells and other changes that much resemble, though they are not identical with, cirrhosis as seen in man.

It behooves us, therefore, to discountenance, as far as possible, the use of the terms atrophic and hypertrophic, since a large liver may be atrophic to a noteworthy degree, and hypertrophy of the liver cells is a conspicuous feature of all small livers. Difficulties in the way of a satisfactory classification, however, are many, of which not the least important is the fact that different etiologic factors may cause similar changes in the liver (so-called atrophic cirrhosis with and without antecedent alcoholism), that one factor may give rise to different forms, so-called, of cirrhosis (thus, so-called atrophic cirrhosis, fatty cirrhosis, and hypertrophic cirrhosis may be preceded by definite alcoholism), and that many factors may be operative in the one case. Probably heretofore we have been too much concerned with the size of the liver, which, nevertheless, is a conspicuous clinical feature; but progress is more likely to be achieved by search for the etiologic factor than by too much attention to more or less disquieting clinical signs, and we have reason for believing that an organ like the liver which possesses really remarkable inherent capabilities for repair might, although considerably damaged, be able to establish functional sufficiency were the etiologic factor, whatever it may be, corrected or removed early—rather earlier, however, than the disease is usually recognized at the present time.

REPORT OF A CASE OF PNEUMOCOCCUS SEPSIS.

By JOHN S. THACHER, M.D.,
OF NEW YORK CITY.

This case is presented as an illustration of the terrible ravages which the pneumococcus may produce throughout the human body in a very short space of time.

The patient, a man aged forty-five years, of excessive alcoholic habits, though a gentleman, was sick only nineteen days. During the first twelve days he went through an attack of acute lobar pneumonia of severe type. There was then a distinct improvement, not by crisis, however, but gradual and not complete. The signs of pneumonia shrank to a very small area.

Five days before his death he showed the first signs of fluid at the base of the same lung, which later proved to be purulent.

Two days before his death the first signs of heart involvement appeared, diastolic murmur and a large, soft pulse with a thrill, followed later by others and loud murmurs, the heart at autopsy showing marked ulcerative endocarditis.

The same day, two days before death, the first signs of meningitis appeared —severe headache and congested eye—but this complication was not suspected until the following day, the day before death, when the neck was stiff. The autopsy showed a very intense meningitis.

The fluid from the chest and from the spinal canal, as well as the blood taken during life, showed an abundant pure invasion of pneumococci.

Taking the illness now in detail, beginning with the pneumonia, we find that on the first day he simply felt a little miserable. On the second day he had a chill, was prostrated, ached throughout the body and took to his bed. He had on that day a little cough, with some expectoration, which seems to have been mucopurulent. On the fifth day of his illness he became delirious, with great mental depression. It was not until the sixth day that he felt pain in his chest, which was quite sharp on deep inspiration. On this day, the sixth of his illness, he came into the hospital very sick. He was irrational, very tremulous, much prostrated, with considerable dyspnea and cyanosis. The pulse was, however, strong, regular, of good size and soft, with a rate on that day between 90 and 100.

The examination of the lungs discovered typical signs of pneumonic consolidation of the right lower lobe, with numerous subcrepitant rales. There

was also a faint bronchial character to the expiratory murmur over the posterior part of the upper lobe on the same side, and over the posterior part of the left upper lobe and the upper part of the left lower lobe, but this was very likely a transmitted quality from the consolidated right lower lobe, and no development of disease followed in these parts. The abdomen was distended, hard and tympanitic. On the following day, the seventh of the illness, he is reported to have stopped breathing for one minute at 5 A.M., but he resumed that function without further interruption.

During the first four days in the hospital, that is, the sixth to ninth days of the illness, he was an extremely sick man, delirious, dyspneic, cyanotic; the temperature ranging gradually higher, up to 104°, the pulse becoming more rapid, though only to about 120 and less strong.

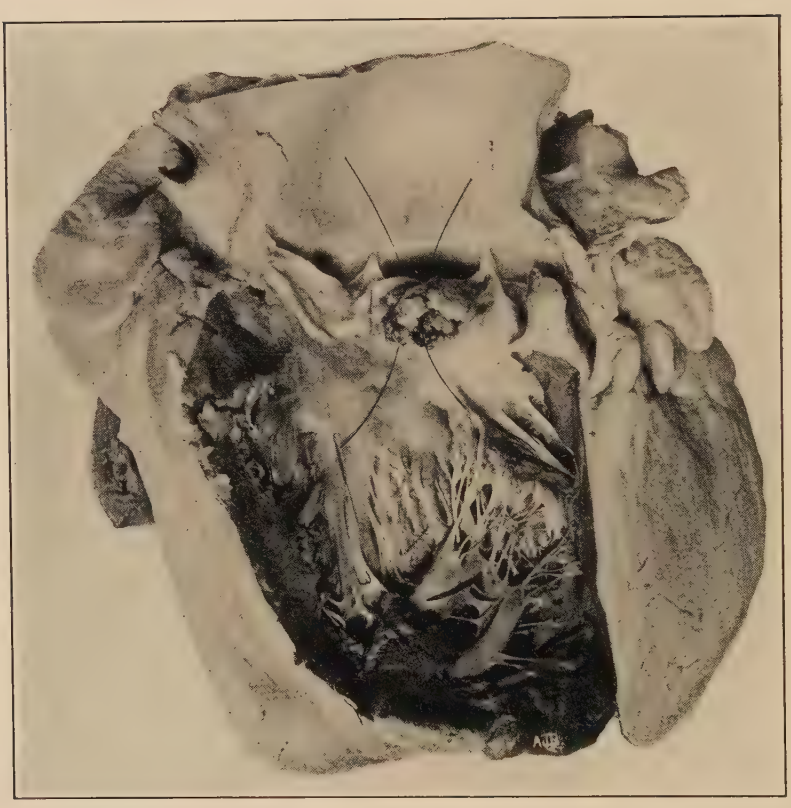
The first sign of improvement was in the abdomen; on the last of these days, the ninth of the illness, it became softer. The following day, the tenth, there was distinct improvement; he became quiet and rational; the temperature came down to 101.5°; the pulse to 96. The next day the signs of consolidation had diminished in area, and on the day after that, the twelfth of the illness, had shrunken to a small area just inside the angle of the scapula. The pulse at this time had improved, its rate coming down on the thirteenth day to 84, while the temperature, with some irregularities, came down to 101.5°.

On the fourteenth day, however, signs of fluid appeared in the right chest, dulness at the base, and faint bronchial breathing over the whole of that left lower lobe. The temperature also began to rise again, and the signs of fluid advanced. Two days later the dulness was noted as higher; there was diminished bronchial voice and breathing, and diminished fremitus at the base without any rales. The heart apex also began to move toward the left, being now four and three-quarter inches to the left of the middle line, instead of four and one-quarter inches, where it was located on the day of his admission. The next day the dulness extended to the angle of the scapula, and the voice at the middle scapular region had a nasal quality. There was very faint bronchial breathing over the back of the left upper lobe, but this was believed to be transmitted from the right side. The apex beat was now five and one-quarter inches to the left of the middle line. The right pleura was aspirated on this day, and 300 c.c. of turbid, greenish-yellow fluid obtained. This fluid, after standing, showed 50 per cent. of puruloid sediment and contained pneumococci and no other kind of bacteria. The pneumococci were identified by their characteristic microscopic appearances, including the capsules, and by the coagulation of Hiss' inulin medium.

The apex beat was found on the next day to have returned to a point four and one-quarter inches to the left of the middle line—that is, to the position which it occupied on the day of admission—one inch within its position before aspiration. The lung became resonant on percussion again down to the base, the respiratory murmur, however, remaining faintly bronchial.

The first evidence of cardiac complication was noticed only two and one-half days before death, when a diastolic murmur was heard at the apex. Up to that time the heart sounds had been clear; the pulse, which had quieted

Fig.



Left ventricle, showing vegetations on the aortic valve. Hairs pass through a small and a large perforation.

down with the resolution of the pneumonia, had not until this day passed 100 again, though there had been a slight increase in the rate during the two preceding days. The day before the murmur was first heard it had been noted that the pulse was good. This murmur, when first heard, was at the apex rather late in diastole, was very faint and of a rumbling quality, and was put down as an early presystolic murmur. The radial pulse became softer and had an appreciable thrill, but its rate was only 102. The apex beat on this day, as on the previous day, had been discovered to be moving outward from four and one-quarter inches to the left of the middle line, where it was on admission, to four and three-quarter inches on the previous day, and five and one-quarter inches on this day. These changes in position were probably due to empyema, for the apex impulse returned after the aspiration to its original position. The right border, however, at this time seemed to have moved a little toward the right, having been noted on admission as normal in position on the day before the murmur appeared as at the middle line, and on this day at the right edge of the sternum. On the following day it appeared to be a little farther to the right. There seems to have been, therefore, some enlargement by this time. On the day after the murmur was first heard the pulse became more rapid, reaching the rate of 114, bounding, quickly collapsing, and with a marked thrill. On grasping the calf of the leg the thrill was very striking. A double murmur was now distinctly heard at the base of the heart on this the next to the last day. The next day, the patient's last, this double murmur could also be heard at the apex, and it was thought that a presystolic murmur was also heard.

The first evidence of meningitis appeared two and one-half days before his death; that is, at the same time with the first evidence of endocarditis. On this day there were severe headache and congestion of the conjunctiva of the left eye. An anxious expression, too, came into the patient's face. The next day the patient was in a semicoma, being hard to arouse; the neck was stiff; there were movements of the left leg seemingly automatic; Kernig's sign was not present. On the next day, the day of death, the neck became more rigid, the Kernig sign was present; a lumbar puncture withdrew three ounces of purulent fluid, which contained an abundance of pneumococci, presenting the same characteristics as noted in the cocci of the pleural fluid.

On the same day, before the patient's death, bouillon tubes were inoculated with the patient's blood, and characteristic growth of pneumococci developed in the bouillon, and, after transplantation, on blood serum and in Hiss' inulin medium.

During these last three days the general condition of the patient naturally became worse gradually and progressively, the temperature was most of the time between 105.6°, the pulse ran up to 150, and the respirations at one time during the last day were 72.

The leukocytes during his stay in the hospital were counted seven times and ranged between 13,500 and 36,000, the highest number being on the eighth day of his illness, the lowest two and one-half days before death, but on the day before death they rose again to 20,000.

The urine on the seventh day had a specific gravity of 1029, and contained 0.5 per cent. of albumin by bulk and some hyaline, granular and epithelial casts. On the thirteenth day the specific gravity was 1016; no albumin or casts were found. On the sixteenth day the specific gravity was 1015; there was a very faint trace of albumin, but no casts.

Before the onset of this illness the patient is said to have been in good health, though often indulging too freely in alcohol. The pneumonia, therefore, seems to have come upon him out of a fairly clear sky, and to have run a course not varying greatly from the ordinary except as modified by his alcoholic history, and to have resolved, though slowly and incompletely. When the pneumonia had nearly resolved an empyema developed, and immediately after this a general infection by pneumococci, which attacked the lining of the heart and the membranes of the brain and spinal cord so viciously that within a very few days extreme lesions were produced of ulcerative endocarditis and meningitis, the chief interest of the case arising from the rapidity and the intensity of the effects of the virulent infection by the pneumococci.

The autopsy, made twenty-seven hours postmortem, revealed a resolving pneumonia, an empyema, an exuberant vegetative and ulcerative endocarditis and an intense meningitis.

The pericardium was normal, the heart muscle showed some grayish mottling. On one of the cusps of the aortic valve was a large, soft, rounded vegetation, half-inch in diameter, with a rough surface and a small perforation through its center. Just beside it there was another perforation through the cusp. The under surface of the adjacent cusp is a little roughened. The heart weighed thirteen and one-half ounces. The other valves were normal.

The left pleura was normal, and the left lung on section showed only a considerable degree of edema. The right pleura, both visceral and parietal, over the entire posterior surface of the lung, was covered with a layer of shaggy fibrin, and in the pleural cavity 175 c.c. of purulent fluid. The lung on section was edematous and congested in the upper lobe, and in the lower lobe dark red, a little mottled, rather granular, tough and flabby, and fragments of it sank in water.

The liver and spleen and pancreas appeared normal.

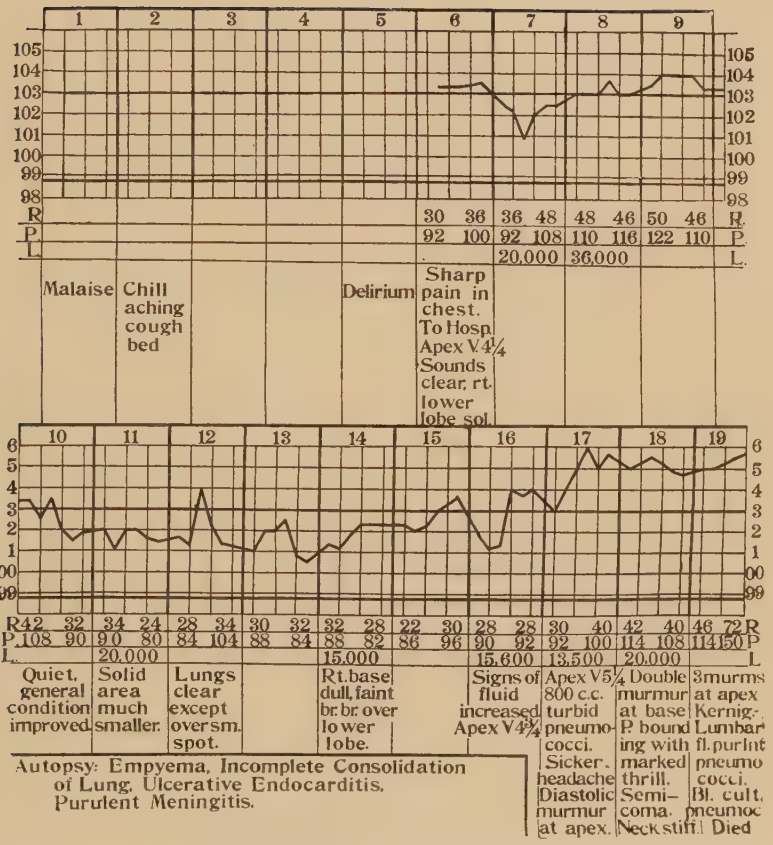
The left kidney showed one little white infarct at the surface and running in about one inch. Otherwise the kidneys appeared normal, excepting some grayness of the cortex on section and congestion of the veins of the surface.

The stomach, intestines and bladder were normal.

Over the brain the pia and arachnoid there was an extremely abundant exudate, quite general, including the convexity, but most marked at the central focal portion. There were numerous petechial hemorrhages in the walls of the fourth and lateral ventricles and a few drops of pus in the lateral ventricles.

Ten blood-serum tubes were inoculated from the blood of the right and left ventricles and from the pericardium. On one of these inoculated from the left ventricle a growth appeared of pneumococci giving the characteristic reaction with Hiss' inulin medium.

FIG. 2


1 2 3 4 5 6 7 8 9
105 104 103 102 101 100 99 98
R 30 36 36 48 48 46 50 46 R.
P 92 100 92 108 110 116 122 110 P.
L 20,000 36,000 L.
Malaise
Chill aching cough bed
Delirium
Sharp pain in chest. To Hosp. Apex V 4¼ Sounds clear, rt. lower lobe sol.
10 11 12 13 14 15 16 17 18 19
6 5 4 3 2 1 00 99
R 42 32 34 24 28 34 30 32 32 28 22 30 28 28 30 40 42 40 46 72 R
P 108 90 90 80 84 104 88 84 88 82 86 96 90 92 92 100 114 108 114 150 P
L 20,000 15,000 15,600 13,500 20,000 L
Quiet, general condition improved.
Solid area much smaller.
Lungs clear except over sm. spot.
Rt. base dull, faint br. br. over lower lobe.
Signs of fluid increased. Apex V 4¾
Apex V 5¼ 800 c.c. turbid pneumococci. Sicker. headache Diastolic murmur at apex.
Double murmur at base P. bound ing with marked thrill. Semi–coma. Neck stiff.
Murmurs at apex Kernig- Lumbar fl. purlnt pneumococci. Bl. cult. pneumoc Died
Autopsy: Empyema, Incomplete Consolidation of Lung, Ulcerative Endocarditis, Purulent Meningitis.

Temperature chart with synopsis of symptoms.

A CONTRIBUTION TO THE STUDY OF THE ETIOLOGY OF TROPICAL ULCER.

By RICHARD P. STRONG, M.D.,
DIRECTOR OF THE BIOLOGICAL LABORATORY, BUREAU OF GOVERNMENT LABORATORIES, MANILA.

In May, 1903, Leishman, in making smear preparations from the spleen pulp of a case of so-called dum-dum fever, was struck by the curious appearance among the spleen cells and red corpuscles of enormous numbers of small round or oval bodies two to three microns in diameter, which corresponded to nothing he had previously met with or had seen figured or described. They stained faintly with methylene blue and with hematin, showing with these stains a sharply contoured or oval shape, but no detailed structure; but on staining them by Romanowsky's method they were found to possess a quantity of chromatin of a very definite and regular shape, which clearly differentiated them from blood plates or possible nuclear detritus. This chromatin appeared in the form of a more or less definitely circular mass or ring, applied to which, although apparently not in direct connection with it, was a much smaller chromatin mass, usually in the form of a short rod set perpendicularly or at a tangent to the circumference of the larger mass. The outline of the sphere or oval inclosing these masses of chromatin was only faintly visible by this method of staining. These little bodies were scattered freely among the cells, as a rule isolated one from the other, but here and there aggregated into clumps composed of twenty to fifty members.

Leishman was unable to say what these bodies were at the time, but later, when working with nagana, upon investigating the blood and internal organs of a white rat dead of this disease he found bodies practically identical in shape and staining reac-

tion with those he had encountered in the spleen of his case of dum-dum fever. He concluded that these parasites were degenerative forms of a species of trypanosoma and that probably this particular case of dum-dum fever represented an infection with this organism.

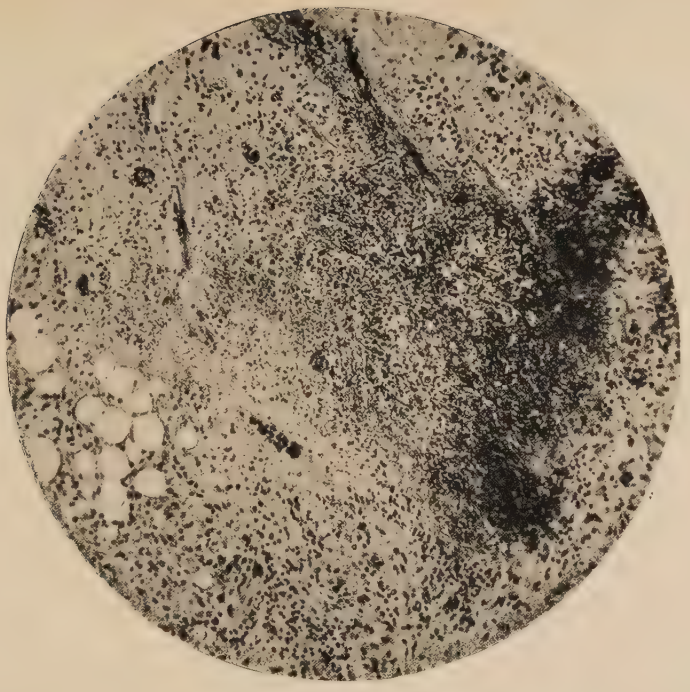
Donovan was the next one to observe these bodies, and, later, Ross and Laveran also reported in regard to the parasites. Ross inclined to the belief that they were sporozoa, while Laveran, who found them inside the red blood cells, concluded they belonged to the genus piroplasma. Later, Marchand and Leidingham, Manson and Low, Bentley and Christophers all contributed cases of dum-dum fever, Kalazar, or splenomegaly, infected with these parasites. Marchand and Leidingham inclined to the original idea of Leishman that they were of trypanosomal origin.

In 1903 J. Homer Wright, in investigating a case of Delhi boil, encountered similar bodies, which he carefully described. Wright believed them to be microsporidia and proposed the name "Helcosoma tropicum." Finally, Leonard Rogers and Chatterjee have stated that trypanosomata have developed in their cultures of the Leishman-Donovan bodies. These parasites have been found in the spleen, liver, bone-marrow, intestinal ulcers, lymph glands and ulcers of the skin, and, according to Laveran and Donovan, within the red blood cells.

After perusing carefully all of the articles of the various observers on this subject, and particularly on comparing their different illustrations, the questions arise: Are the bodies described in all cases identical and what is their origin and nature? Are they forms of a trypanosoma, are they piroplasmata or sporozoa or some other form of parasitic life?

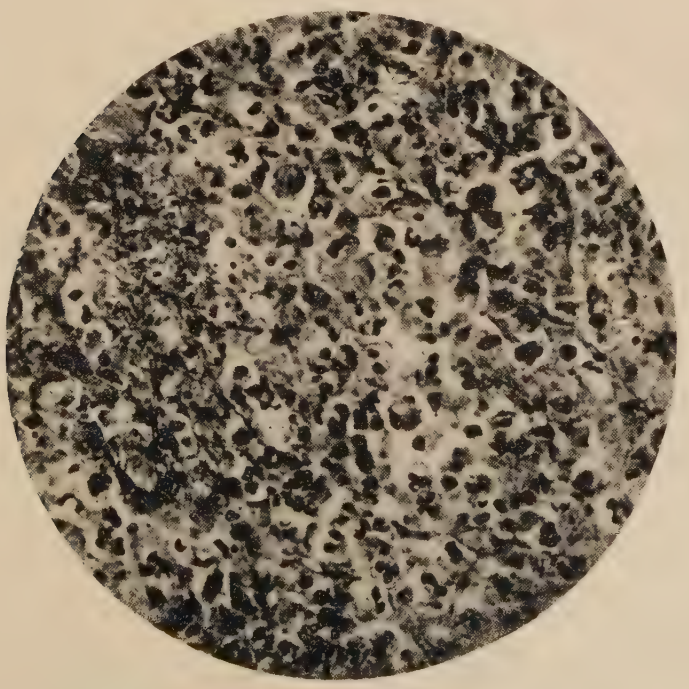
The observations which are to be here recorded are the result of a study undertaken for the purpose of discovering if any of these bodies were to be encountered in similar diseases which occur in the Philippine Islands. During the past year several of our laboratory staff, Drs. Herzog, Musgrave, Woolley, Wherry and myself, have sought at length for these parasites in cases of splenomegaly and cachexia without finding any organisms that we could absolutely identify with them. I have been examining for some time all cases of boil or ulcer of tropical origin that I have been able to see with the hope of encountering the bodies

FIG. 1



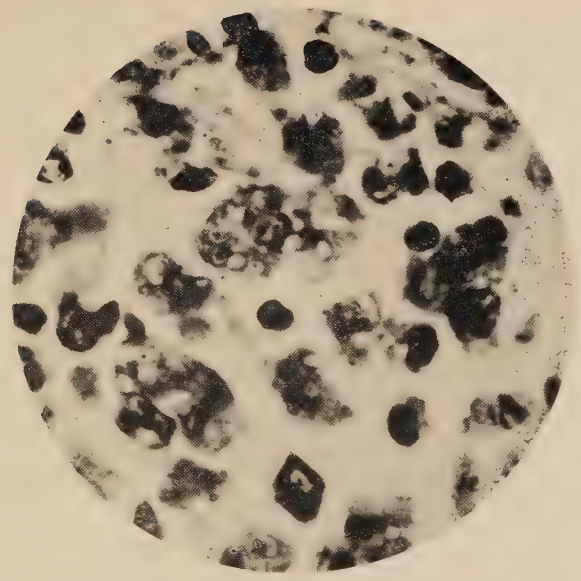
Sections of the subcutaneous tissue showing area of necrosis with extensive cellular infiltration and fibrin formation. In the fibrin mass just to the left of the centre the parasites are very numerous.

FIG. 2



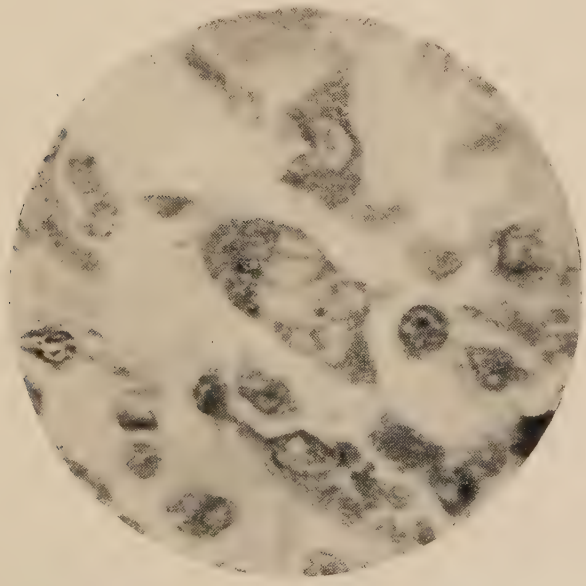
A portion of the same field as Fig. 1, more highly magnified. The parasites may be seen as small stained dots and oval bodies, some lying free, but the majority enclosed in phagocytic cells.

FIG. 3



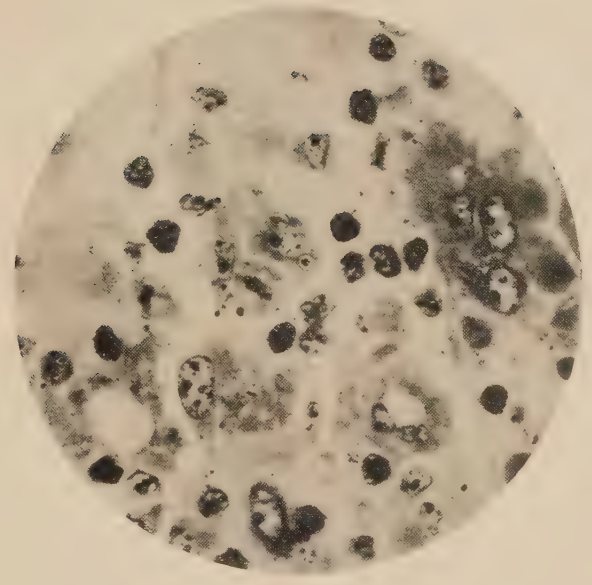
Numerous parasites enclosed in endothelioid phagocytic degenerating cells. The large phagocytic cell situated just above and to the left of the centre of the field encloses a parasite showing the larger mass of chromatin and also the rod-shaped body.

FIG. 4



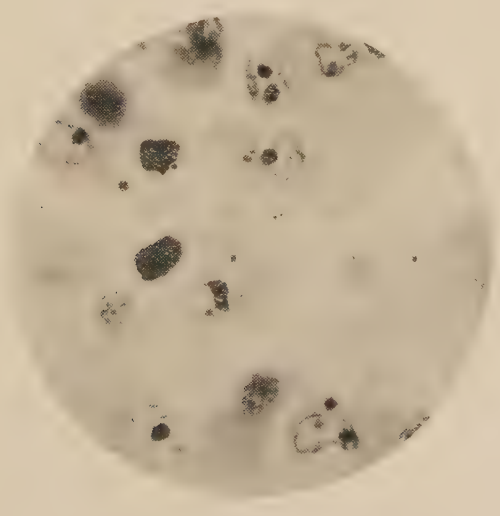
Large phagocytic cell enclosing at least five parasites, in two of which the crescent-shaped deeply staining mass of pigment is in focus.

FIG. 5



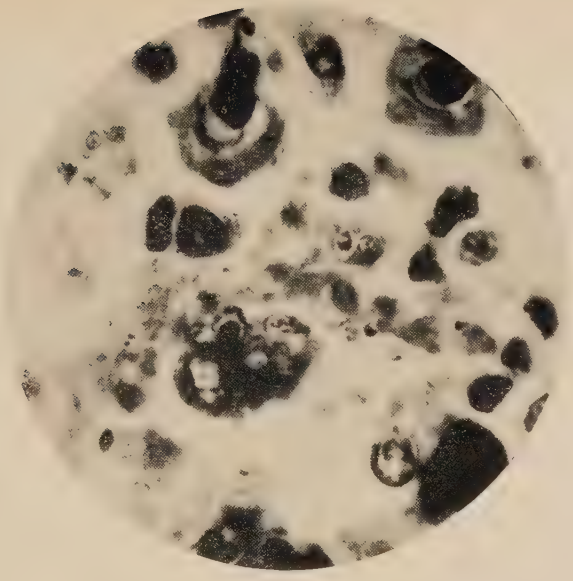
Illustrates particularly two of the parasites not enclosed in cells, one lying almost in the centre of the field and the other, a "seal-ring" form, lying below the centre.

FIG. 6



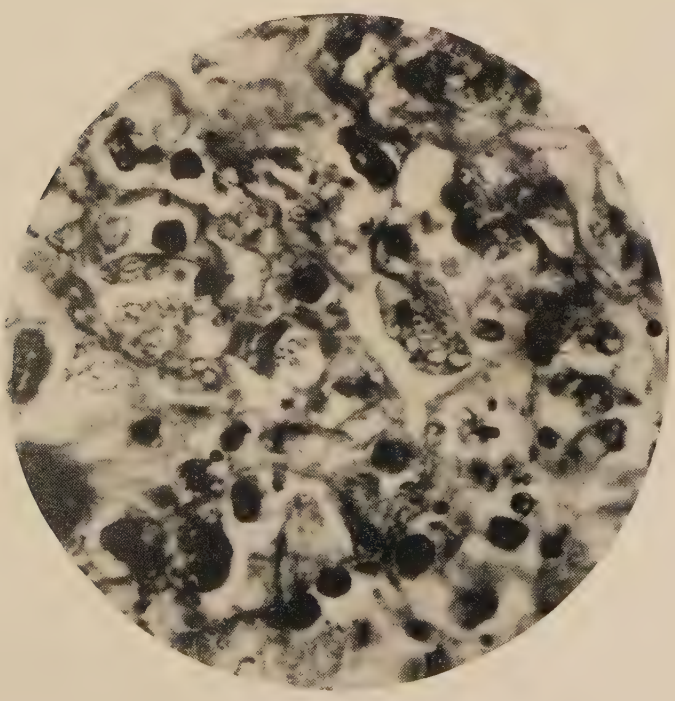
Single parasite with ring of chromatin to which is attached a short rod.

FIG. 7



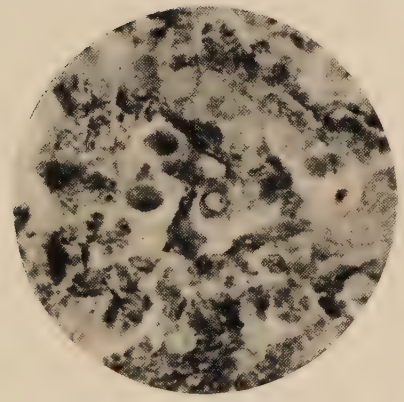
Free parasites and others enclosed in phagocytic cells.

FIG. 8



Numerous parasites, many in clusters which show no stained chromatin masses in focus. Considerable fibrin formation is evident.

Fig. 9



Showing particularly single parasite in the centre of the field.

Fig. 10

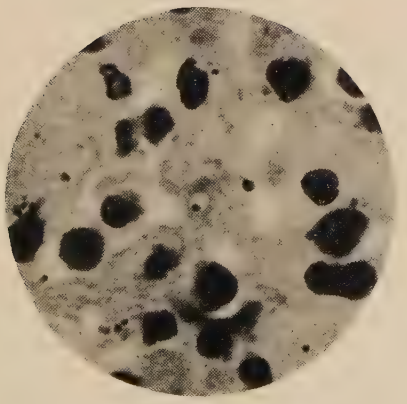
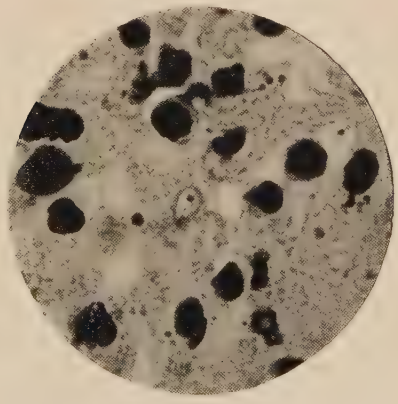
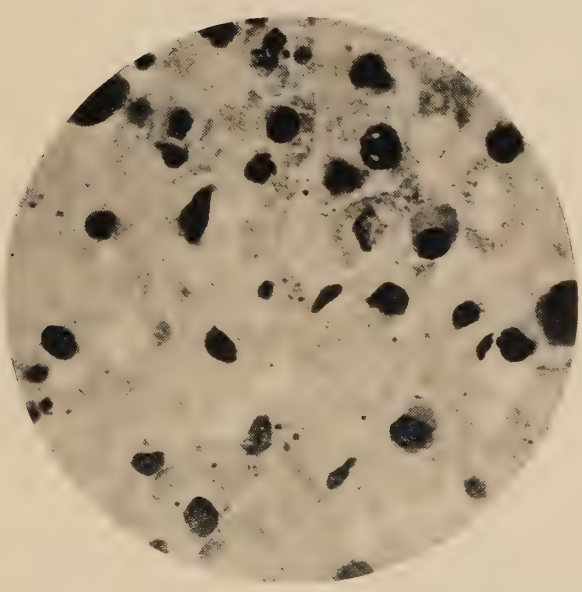


Fig. 11



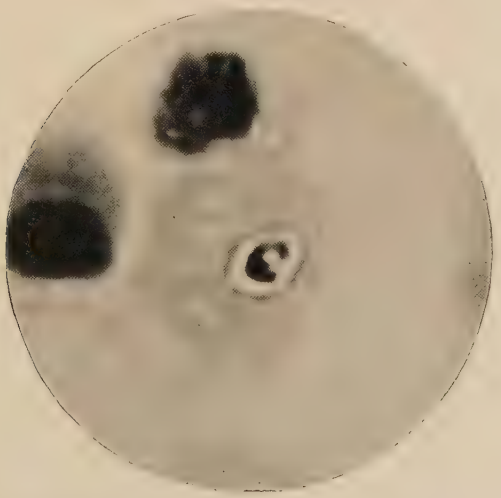
Leishman-Donovan bodies in a smear from the spleen; photograph from one of Major Leishman's specimens; section sent through the kindness of Dr. Koch. The parasites in the centre were selected to show the sharp outline of the limiting membrane.

FIG. 12



Numerous Leishman-Donovan bodies; photographed from the same specimen as Figs. 10 and 11. The stained chromatin masses are in better focus than the outlines of the parasites in this photograph.

FIG. 13



Single parasite more highly magnified ("seal-ring" form).

which Wright has described. Up to now twenty-four cases have been studied but no organisms identical with those which he has pictured in his article have been discovered. However, in one case bodies have been found which simulate slightly his parasites but which more closely resemble some of those pictured by Marchand and Leidingham.

The history of this case may be briefly recorded as follows: The patient was a native woman about thirty-five years of age. Approximately, six weeks before consulting me she stated that she had noticed a small, red, raised spot on the right side of the chest just below the clavicle and above and to the right of the breast. The lump gradually enlarged in size but occasioned little pain. When I first saw the boil it was about the size of a half-dollar and had not opened. The skin over the centre was scaly, indurated and reddened. Fluctuation could be obtained. On incising the abscess in the centre a scanty, rather thick, purulent material was found and a small, ulcerating cavity was exposed, containing soft granulations. On the following day, under cocaine anesthesia, the whole cavity was carefully curetted. The operation was thoroughly performed, because the patient insisted on leaving the next day for the provinces, to be gone several months. Directions were given for daily antiseptic dressings of the wound. I was unable to see her again until four months later, when, after repeated requests, she finally returned to the city and exhibited a contracted scar, the size of a dollar, situated over the original site of the lesion. She reported that the wound had gradually healed after about two months. Portions of the granulations removed with the curet were hardened in Zenker's fluid, embedded, sectioned and stained in hematoxylin-eosin, hematoxylin-picrofuchsin, methylene blue and eosin, fuchsin, Borrell's stain and Wright's modification of Romanowsky's method. The photomicrographs are made from these sections.

The histologic changes consist, briefly, of a chronic inflammatory process in the subcutaneous tissue, with areas of acute inflammation showing cellular infiltration and necrosis and considerable fibrin formation. There is extensive proliferation of the endothelial cells of the lymphatic vessels, together with proliferation of the fixed connective-tissue cells. Multinuclear giant cells are not uncommon and plasma cells are fairly numerous. A

striking feature is the presence of numerous large endothelioid phagocytic cells. No bacteria are evident in the sections. A detailed histologic description need not be given here. Of chief interest is the presence of parasites, which are scattered throughout the tissue. These may be described as oval bodies, resembling "cockle shells," with a sharp outline, measuring about 4μ in their greatest diameter. In sections stained with hematoxylin and eosin they usually remain uncolored; in those stained with picrofuchsin, Borrell's blue or Wright's method they are still mostly uncolored; but many contain particles of chromatin, which stain and which consist, first, of rounded masses, sometimes in the form of a ring, and second of a small dot or rod. These bodies are found both free and also enclosed in large numbers in endothelioid phagocytic cells or lying in a sort of matrix. They are very definite organisms and there is no doubt that they are parasites. In not all of the "cockle-shells" are the chromatin masses present and many of them contain either the ring body or the pigment dot or rod alone; in fact, it is somewhat exceptional to see both chromatin particles in the same parasite. With Zeiss' objective DD and ocular 3 the organisms appear as small dots and oval bodies lying free, but mostly enclosed in phagocytic cells. Their appearance under this magnification is illustrated in Fig. 2.

These bodies are clearly not identical with Wright's parasites, as may be seen by comparison of Wright's photomicrographs with those from my sections. They simulate somewhat some of the forms occasionally seen in Leishman's specimens, one of which is illustrated in Fig. 10. However, when compared with the majority of his parasites (Fig. 12), one sees at once very striking differences. The distinctions between Wright's and Leishman's parasites are also very evident, while in specimens which Rogers has very kindly sent me of the developmental forms, I could not certainly identify his organisms with those of Leishman's specimens. The bodies which are found in my sections simulate more closely some of those pictured by Marchand and Leidingham in their most recent article in the *Zeitschrift für Hygiene*, 1904, but it is doubtful if they are identical with these. Christophers noted that the bodies which he encountered had a very sharp outline and seemed to possess a cuticle.

There can be no doubt as to the nature of the parasites encountered in my sections. They are evidently forms of blastomyces (torulæ), though they are very different from the usual species of blastomyces encountered in certain human skin affections.

After a careful comparison of these bodies with those which have been found in ulcerations of the skin occurring in horses in the tropics suffering from blastomycetic infection, I believe that the parasites of the two diseases are probably identical and, as in glanders, we have a disease which is occasionally transmitted to man; so human beings may also acquire sometimes this equine blastomycosis. Cultures were attempted on agar from the lesion in my patient at the time the tissue was secured, but, although large numbers of the parasites were inoculated, no apparent growth took place during several months. This is another point in favor of the identity of the two affections, since the parasites found in the horse are frequently very difficult or impossible to cultivate. My laboratory investigations have led me to conclude that tropical ulcers have a varied etiology, since I have not encountered any of the bacteria or parasites which have been described by other observers. As exemplified in the case here reported, a somewhat rare form of tropical boil or ulcer is evidently of blastomycetic origin.

CHRONIC ACETANILID POISONING, WITH REPORT OF A CASE DUE TO ABSORPTION OF THE DRUG FROM AN ULCER OF THE LEG.

(ABSTRACT.)

By JAMES B. HERRICK, M.D., and E. E. IRONS, M.D.,
of Chicago.

A woman of fifty for seven years applies daily to a large varicose ulcer of the leg about one ounce of a powder the nature of which is to her unknown. She has during these seven years, especially of late, suffered from more or less weakness, dyspnea, palpitation, mental depression and general "nervousness." On examination she is found cyanotic. The cardiac and pulmonary findings do not explain this cyanosis. The liver and especially the spleen are enlarged. The blood shows a moderate degree of secondary anemia; no methemoglobinemia. The urine is dark in color, contains paramidophenol and an increased amount of ethereal sulphates; no methemoglobin. The powder, by physical and chemical tests, is found to be pure acetanilid. Stopping its application to the ulcer results in complaint of pain, extreme restlessness, with almost maniacal excitement. The reapplication of the powder or the use of the powder or of acetanilid from the drug-room internally quiets the nervous symptoms. By gradual lessening of the amount of the drug applied to the leg the patient is broken of her habit and the use of the drug is finally given up. Marked improvement in the general condition follows, the blood findings become normal, the cyanosis disappears, the spleen diminishes in size, the urine is as in health and there is a great gain in weight.

The study of the case carried on for a period of several weeks showed several interesting facts, among which are the following:

The effect of the chronic intoxication on the general nutrition was marked. Anorexia, irregular action of the bowels, weakness, with considerable emaciation disappeared promptly when the drug was stopped.

The blood did not show methemoglobinemia as reported in some other cases.

The anemia was moderately severe—70 per cent. of erythrocytes, 40 per cent. hemoglobin. Leukocytosis was moderate, 12,000, and was polymorphonuclear in type. Morphologic degenerative changes in the red corpuscles were not pronounced. One month after the use of the acetanilid had been stopped the blood count showed 5,580,000 red corpuscles and 100 per cent. of hemoglobin.

The urine averaged 1800 c.c. with a specific gravity of 1015. Casts, albumin and sugar were absent. No blood, hematin, hematoporphyrin, indican or bile pigments were found. Methemoglobin was absent. Fehling's solution revealed no copper-reducing substances. The urine was dark, in color like port wine, and on standing became brownish black. Cover-glass preparations of bacteria—*e. g.*, B. coli communis, B. typhosus—took a light-brown stain when immersed in the urine for one hour. Connective tissue in celloidin preparations was stained when treated for a short time by urine that had been allowed to stand for several days. The color tests for paramidophenol were positive as was the indophenol reaction.[1] Ethereal sulphates were increased and the mineral sulphates lessened, the ordinary ratio of mineral to ethereal sulphates of 10 to 1 being reversed. A return to the normal proportion followed the withdrawal of the drug.

The enlargement of the spleen was striking, as was its distinct diminution in size when the intoxication was at an end. Feeding acetanilid to animals (rabbits, guinea-pigs and dogs) failed to produce splenic enlargement, except in one dog, where a slight enlargement with connective-tissue increase was found.

The addiction to the use of the drug was as pronounced as in

[1] Neubauer und Vogel, p. 614.

the case of the morphin or cocaine habitué, though more amenable to treatment, which was here entirely successful by the method of gradual withdrawal.

The acetanilid habit is probably more common than is generally supposed; a number of recently reported cases of chronic poisoning seem to indicate this. The ease with which the drug may be obtained by the laity, either in its pure condition or as the main ingredient of patent and proprietary medicines that are sold for the relief of headache and of other pains, makes it probable that milder cases of chronic poisoning due to indulgence in the habit are not infrequent.

The recognition of the condition depends on the detection of the use of the drug, not always an easy matter from the history, as these patients are as prone to deceive as are those addicted to morphin. Otherwise unaccountable cyanosis should arouse suspicion. Alimentary disturbances and neurasthenic symptoms may be due to the poisoning. The enlargement of the spleen has been reported in several cases. Secondary anemia may be extreme and marked degenerative changes in the erythrocytes have been seen. Nucleated reds may be abundant; leukocytosis is common. Methemoglobinemia may be found. Strangely enough, in some cases polycythemia rather than anemia has been reported. One such case in a chronic intoxication from the prolonged use of "Orangeine" has been under my care. The surest aid to diagnosis is the examination of the urine, which reveals the dark color, paramidophenol and increase in the conjugate sulphates.

The condition must be differentiated from diseases that might produce cyanosis, such as cardiac and pulmonary disease, as well as from the anemias and leukemias. Careful study of the blood will clear up these differential points. Cyanosis with polycythemia and splenic enlargement may be simulated by acetanilid intoxication, as may cyanosis that is enterogenic. The study of the urine is here all important as an aid to diagnosis.

Promising fields for investigation are opened up by the recent interest in cases of cyanosis, polycythemia and splenomegaly. Perhaps a study of chronic acetanilid poisoning may throw some light on these cases.

ON GONORRHŒAL SEPTICÆMIA AND ENDOCARDITIS.

By W. S. THAYER, M.D.,
OF BALTIMORE.

The comparative frequency of gonorrhœal septicæmia and endocarditis may be regarded as generally recognized, and, since the positive results obtained by Blumer,[1] Lazear,[2] and the writer,[3] abundant proof of the specific nature of the infection in many of these cases has been accumulated. At the same time the observations of many students have shown that a demonstrable septicæmia may exist in connection with various complications other than endocarditis.

While the communication of Gurvich[4] has made evident the fact that gonorrhœa may be followed by mild forms of valvular disease, those cases which have particularly attracted the attention of clinicians have been instances of grave malignant endocarditis. The clinical picture of these cases differs in no essential particular from that associated with ulcerative endocarditis from other causes.

The development of symptoms suggestive of septicæmia with fatal results, consecutive to gonorrhœa, without evidence *intra vitam* of any focal complication, is also an occurrence of no great

[1] Thayer and Blumer. Endocardite ulcéreuse blennorrhagique. Septicémie d'origine blennorrhagique. Arch. de méd. exper. et d'anat. pathol., 1895, vol. vii., p. 701; also, Johns Hopkins Hosp. Bull., Baltimore, 1896, vol. vii., p. 57.

[2] Thayer and Lazear. A second case of gonorrhœal septicæmia and ulcerative endocarditis with observations upon the cardiac complications of gonorrhœa. Jour. Exper. Med., New York, 1899, vol. iv., p. 81.

[3] Thayer. Gonorrhœal endocarditis and septicæmia. Compt. rend. cong. internat. de méd., 1897, Mosc., 1899, vol. iii., 5 sec., p. 350–367.

[4] Russk. Arch. Patol. klin. Med. i. Bakt., 1897, vol. iii., p. 329.

rarity. In most of these instances, however, necropsy reveals some local focus of infection outside of the urethra. Dr. Osler, for instance, tells me of a case of lethal septicæmia consecutive to gonorrhœa, which presented, during life, no localizing symptoms, where, at necropsy, the only focal lesion to be found was a prostatic abscess no larger than the end of the thumb. A similar case was under my care thirteen years ago, in which, however, no necropsy was obtained. A young man of twenty-two developed, in connection with an acute urethritis, an intermittent fever of extreme severity. Observed for several weeks in the hospital, the heart sounds were perfectly clear, and no evidence of any localization of the infection was to be detected beyond the history of a very slight arthritis, which had entirely cleared up. The patient died several weeks after leaving the hospital.

Padula,[1] in 1892, described a form of mild continued or intermittent fever which he had observed in a number of instances of gonorrhœa, sometimes in simple cases, but more particularly in those with complications. After running a course of several weeks' duration the fever disappeared.

From our present knowledge of the biological characteristics of the gonococcus it is natural to regard these cases, both mild and severe, as instances of true septicæmia. While this is well known to be the case in the more severe cases, the proof of the existence of septicæmia has not as yet been afforded in the milder instances.

It was, however, our good fortune last summer to observe an instance of continued fever of about seven weeks' duration occurring in a case of acute gonorrhœa, without apparent complications, in which the existence of a septicæmia was established by cultures from the blood. The case will be described later in this communication.

Our experience with gonorrhœal endocarditis and septicæmia in the Johns Hopkins Hospital has been rather interesting. Apart from the eight cases reported by Blumer,[2] Lazear,[3] Harris and

[1] Febbre infettiva da virus blennorrhagico. Roma, 8vo., 1892.
[2] Op. cit.
[3] Op. cit.

Dabney,[1] Johnston,[2] and myself,[3] there have occurred two recent instances of ulcerative endocarditis of gonorrhœal origin, to which I shall refer later, making in all six cases in which gonococci were positively identified by cultures from the blood *intra vitam* (Thayer and Blumer), from the local lesions at necropsy (Harris and Dabney, Case I.; Thayer, Case II. of this communication), or by both methods (Thayer and Lazear, Harris and Johnson, and Thayer, Case III. of this communication).

In one case (Harris and Dabney, Case II.) the presence of characteristic organisms at necropsy, taken in connection with the absence of growths on ordinary media, afforded almost positive proof of the specific nature of the infection.

In three cases (Thayer and Lazear, Case XXXII. of the table, and Harris and Dabney, Cases III. and IV.), with an evident mixed infection, organisms were found at necropsy microscopically and tinctorially characteristic of gonococci. In one of these (Harris and Dabney, Case III.) diplococci, morphologically and tinctorially characteristic, were found in the pericardium, while cultures from the same source were negative. In the other two cases, although the cultures from the valves showed other organisms, the infection clearly followed an acute gonorrhœa without other apparent cause.

In addition to these instances I have, in the past six years, seen in consultation four cases in which an ulcerative endocarditis has followed gonorrhœa. In only one of these instances were cultures taken *intra vitam*, and here streptococci were obtained. In one other, in which the necropsy revealed an ulcerative mitral endocarditis, an unidentified bacillus was cultivated. In all of these cases, however, the connection of the urethritis with the development of the symptoms was such as to make it probable that the acute infection had served as the portal of entry. Such an experience as this is sufficient to emphasize the fact that an acute urethritis is by no means infrequently followed by an endo-

[1] Report upon a case of gonorrhœal endocarditis, etc. Johns Hopkins Hosp. Bull., Baltimore, 1901, vol. xii., p. 68.

[2] Harris and Johnston. Gonorrhœal endocarditis, with cultivation of the specific organism from the blood during life. Johns Hopkins Hosp. Bull., Baltimore, 1902, vol. xiii., p. 236.

[3] Op. cit.

carditis, either of specific gonorrhœal nature or due to secondary or mixed infections which have found their portal of entry in the urethritis or have settled later upon the primarily infected valves.

The last two hospital cases, which will be reported at the end of this communication, presented the usual features of ulcerative endocarditis—irregular, intermittent fever, chills, progressive anæmia, and nephritis—developing on the one hand in a case of acute gonorrhœa with arthritis about five weeks after onset, and in the other during a demonstrable urethritis, which the patient, a colored man, denied. It is interesting that in both of these cases, with a pure aortic lesion, there was a well marked, presystolic, rumbling (Flint) murmur, suggestive of mitral involvement. In one of the cases, indeed, a diagnosis of mitral disease was made. Cultures from the blood during life were positive in one, negative in the other. In both cases pure cultures of the gonococcus were obtained at necropsy from the affected valves.

The remaining case, which is regarded as of especial importance, is an instance of gonorrhœal septicæmia, with continued fever of seven weeks' duration.

Case I.—*Male, aged twenty-eight years; gonorrhœa; posterior urethritis; continued fever of seven weeks' duration suggestive of typhoid; gonococci obtained in pure culture from the circulating blood; recovery.*

Hospital No. 47,439; Medical No. 17,342. X., aged twenty-eight years, was admitted to the Johns Hopkins Hospital on 17th July, 1904, complaining of headache, fever, and a general "run-down" condition.

Family History. Mother, living and well. One brother has some trouble with his stomach. One brother and one sister died in infancy. Family history, otherwise good.

Previous History. Has always been strong and well. As a child, had scarlet fever, chicken pox; thinks that he had typhoid fever at the age of six or seven. Eight years ago he had two sores on his penis which were said to be chancres. He was treated constitutionally and had no secondary symptoms. Later, he has been assured by physicians that the lesions were chancroidal. Four years ago he had an attack of gonorrhœa with posterior urethritis. Three months ago, had a second attack, which has continued active to the present time. Has been a moderate drinker until eighteen months ago, since when he has been abstemious.

Present Illness. On 10th July, on the first day of a vacation, while in the country, he was seized with a severe headache and fever; no chills. On the following day he was seen by Dr. S. Sydney Kellum, of Bellhaven, Virginia, who found that he had a temperature of 103.5° and was restless, complaining of severe pains in his head and back. He complained of having felt "weak and bad" for a week or so. The tongue was coated; the pulse about 90. The patient was given a laxative. On the following morning the temperature was 99.8°. He was up and about. R—Quin. sulph., gr. iv, every four hours. In the afternoon, however, his temperature was 102.6°. On the three following days the condition was about the same On the evening of the 15th of July the temperature was 103.6°. The splenic dulness was slightly increased and there was some tenderness on pressure. On entering the hospital the patient had complained only of severe headache, fever and constipation. His mind was much taken up with the fear that he had lues.

18*th July*, 1904. Red blood corpuscles, 5,024,000 to the cubic millimetre; leucocytes, 9000 to the cubic millimetre; hæmoglobin, 92 per cent. Smears from the urethral discharge, which was fairly profuse, showed large numbers of gonococci.

19*th July*. On this date Dr. Cole noted that the patient was well nourished; face flushed; mental condition quite clear and bright. He moved himself in bed readily and did not appear very ill. The tongue had a thick yellow coat; pupils widely dilated. The chest was well formed; expansion good and equal; everywhere resonant. Auscultation, clear throughout.

Heart. Point of maximum impulse was seen and felt in the fourth interspace just inside the mammillary line. The dulness extended just to this point. There was no dulness to the right of the sternum. The heart sounds were everywhere clear and regular. Pulse regular, 23 to the quarter, of good force and volume; no dicrotism. The vessel wall was not thickened. The *abdomen* was full, though not distended. There was no abdominal pain; no tenderness. The edge of the *spleen* was felt about a finger's breadth below the costal margin, hard and not tender. Over the entire body, especially on the chest and thighs and also on the face, forearms and hands there was a diffuse slight mottling of the skin. At places these small bodies are slightly raised, particularly on the forearms; no characteristic rose spots. There was a slight urethral discharge.

20*th July*. On this date I saw the patient, noting that the spleen was distinctly palpable, well below the costal margin.

23*d July*. Leucocytes, 8900. The temperature had ranged daily between 99° and 103° with regular morning remissions. The blood was negative for malarial parasites. On the evening of the 23d the temperature reached 103.8°, being affected little by sponging. After an ice sponge at 10 o'clock at night, however, the temperature fell to 98.4°, rising, however, soon afterward to 102° at 4 A.M. There was a slight chill on the afternoon of the 23d.

24th July. Dr. Cole noted that the lungs were clear throughout.

Heart. Impulse not seen or felt. Sounds best heard in the fourth and fifth spaces just inside the mammillary line; clear. Pulse, 27 to the quarter, of moderate volume and tension, a trifle irregular.

25th July. The temperature remained elevated, being 101.2° at eight in the morning. Fresh and stained blood was negative for malarial parasites. On this date Dr. Thayer noted that the patient was in good condition. The tongue had a pasty coat; the abdomen was natural.

Heart Apex impulse is not sharply defined; it is, however, felt just outside the mammillary line, in the fifth space, 12.5 cm. from the midsternal line. The dulness extends 0.5 cm. outside of this and 4.5 cm. to the right, the greatest diagonal dulness being 15 cm. The sounds, loudest at the point of maximum impulse, are clear excepting for a slight reduplication of the first sound which is rather better heard over the right ventricle. In the pulmonic area the second sound is sharp and clear, no reduplication. The sounds are also clear in the aortic and tricuspid areas.

On the 26th, the patient complained slightly of a sore throat, the pharynx being a little injected. The right tonsil was slightly swollen with two small white follicular plugs. The pulse was about 25 to the quarter, of good quality, regular, nothing new on examination of the heart. There were a few rather suspicious papules on the abdomen suggestive of rose spots although not wholly typical. There was no tenderness and no distention of the abdomen. Widal tests, made on the 21st and on this date, were entirely negative. A rectal examination showed that the prostate was small, soft and rather tender. There were no nodules in the seminal vesicles. There was a marked right varicocele, while the left epididymis appeared to be somewhat indurated near the globus minor.

The temperature, which had been above 104° on the two preceding days, fell lower in the morning, rising only to 103.6° at night. On the 27th the general range was a little lower. The leucocytes were 9000 to the cubic millimetre.

28th July. It was noted by Dr. Thayer that the heart sounds were clear at the apex and base and in the tricuspid area. At the end of inspiration the first sound in the pulmonic area was a little prolonged.

The diagnosis throughout had been regarded as lying between a gonorrhœal septicæmia associated with an endocarditis, or typhoid fever. Despite the slight increase in leucocytes we had been growing more inclined to regard the case as one of typhoid fever. It was deemed wise, however, on this date, to take cultures from the circulating blood. These were accordingly made by Dr. Brush. 1.5 c.c. of blood were therefore withdrawn in the usual manner from the median basilic vein, from which two agar plates were made. The vein was then cut down upon and about 7.7 c.c. obtained from which one agar plate was made.

At 8 P.M. on this day the patient complained of pain in the lower præcordium, and to the right of the sternum. No friction rub, however, was heard.

29th July. The temperature still remained elevated, ranging between 99.6° and 102.8°. The spleen was readily palpable. The heart sounds were quite clear. There were several suspicious rose spots. Pulse, 22 to the quarter, regular, not dicrotic. During the next several days there was little change in the condition of the patient.

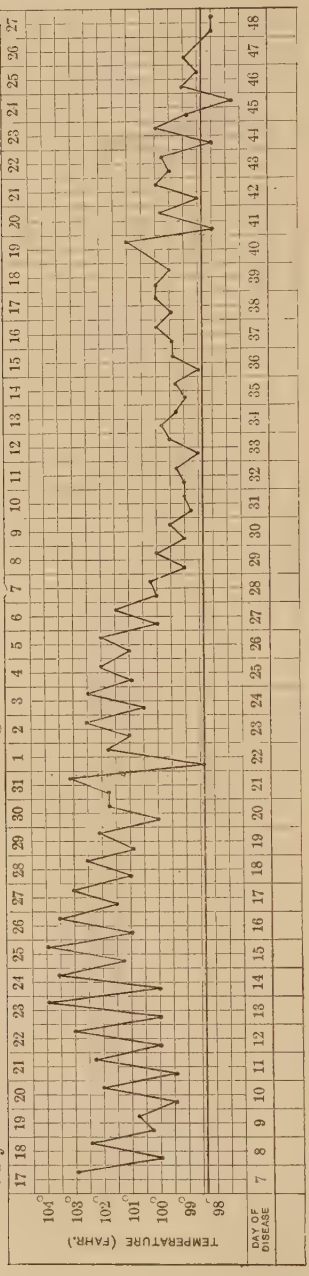
Results of cultures taken on 28th July. In twenty-four hours there was a diffuse growth of minute grayish colonies on the first two plates, those in which the smaller quantity of blood was used. In the third plate there were a very large number of colonies of *bacillus subtilis*, a contamination. Subcultures on blood agar from the first two plates yielded a faint growth of discrete, pin-point, almost translucent colonies composed of a diplococcus, which was almost entirely decolorized by Gram. Transferred to agar there were, in twenty-four hours at 37°, many pin-point, discrete grayish colonies unchanged in forty-eight hours and twelve days. On the plain agar slant there were very delicate, pin-point, slightly elevated, translucent islands along the smear. No change in forty-eight hours or twelve days. There was no growth on glucose agar, potato, bouillon, or litmus milk. The colonies consisted of biscuit-shaped diplococci growing in pairs, tetrads and short chains. They were immobile and decolorized by Gram's method. The cultural as well as the morphological and tinctorial characteristics justified the diagnosis of gonococcus.

From this time on there was a gradual fall in temperature. On 3d August, the temperature at eight in the morning, was 100.5°; leucocytes 12,000 to the cubic millimetre. The patient had been fairly comfortable, though there was a regular evening exacerbation of the fever and often slight chilly sensations. There was some little headache. The urethral discharge had disappeared.

4th August. On this date, Dr. Cole noted that the pulse was of good quality, 24 to the quarter; the tongue was still coated; the spleen readily palpable; the heart sounds clear. During the 6th, 7th and 8th the temperature gradually fell. On the 9th the highest point reached was 99.6°. On this date Dr. Cole noted that the patient's general condition was excellent; the tongue was clean; the heart sounds were clear. For the two preceding days the patient had complained of slight pain in the lower abdomen, but there was little or no tenderness and no distention. Leucocytes, 10,000 to the cubic millimetre. From this time on the temperature remained below 100°, excepting for a slight exacerbation to 100.8° on the 19th and to 100.4° on the 24th.

On 28th August it was noted that the point of maximum cardiac impulse was in the fourth interspace, 9.25 cm. from the midsternal line, the dulness reaching about to that point and 3.5 cm. to the right at the fourth rib. There was a slight cardio-respiratory souffle at the apex and a very slight scratchy

FIG. 1



CASE I.—Gonorrhœal septicæmia.

murmur along the left sternal margin and in the pulmonic area. Pulse, 26 to the quarter, frequently a little irregular.

From this time on the patient steadily improved. There remained, however, a slight urethral discharge.

16*th September*. On this date, the day before his discharge, it was noted that the patient's convalescence was uninterrupted; he was gaining rapidly in weight and strength. His color was good. There was slight dyspnœa on walking. The patient was, however, very nervous.

Heart. Point of maximumim pulse not clearly seen or felt. Sounds best heard in the fourth interspace 9.5 cm. to the left of the median line. Relative cardiac dulness extends just to this point and 6 cm. to the left in the third interspace. To the right the dulness extends 5 cm. at the fourth rib. The sounds are well heard, clear and of normal relative intensity at the apex and base. In the pulmonic area there is still a short, rather slight systolic murmur heard over an area a little larger than the bell of the stethoscope and not transmitted. The pulmonic second is well heard, not accentuated.

17*th September*. The patient left the hospital in excellent general condition.

The *urine*, repeatedly examined during the patient's stay in the hospital, showed nothing remarkable, excepting a sediment containing at first much pus, which, however, disappeared in great part later. On several occasions there was a slight trace of albumin.

In response to a letter the patient called to see me on 11th February, 1905. He stated that he had been perfectly well since discharge excepting for the fact that he was still under Dr. Young's treatment for his posterior urethritis. He looked perfectly well. The pulse at the beginning of examination was 22 to the quarter, of fair size and duration, not remarkable in quality. The maximum blood pressure by the Cook instrument with the broad band was 124; minimum about 108.

Heart. Point of maximum impulse, in the fifth space, a trifle inside the mammillary line. Relative dulness at the third rib; extends 2.7 cm. to the right of the midsternum and just outside the point of maximum impulse. Maximum diagonal dulness about 14.5 cm. The first sound at the apex is perfectly clear; second sound, clear. The sounds were also clear at the tricuspid pulmonic and aortic areas excepting for a very soft systolic souffle heard only at the base, louder in the pulmonic area, and an occasional reduplication of the second sound with inspiration, which was more marked on deep breathing. The heart's action is perfectly regular. There is no evidence of any cardiac lesion.

Here, then, was a patient with vague, general symptoms of headache, backache, and general malaise, continued fever, a thickly coated tongue, a palpable spleen, and suspicious rose spots. These general symptoms, which lasted seven weeks, were

not unsuggestive of typhoid fever. In view, however, of the cultures and the course of the case the condition was clearly due to gonorrhœal septicæmia. Our suspicion throughout was that there might be an endocarditis, but at the subsequent examination, five months after his discharge, there was no evidence of cardiac involvement. If an endocarditis was present it must have been of so slight a degree as to leave no appreciable permanent damage.

The main points of interest in these observations would seem to be:

1. The demonstration of the fact that the mild, continued fever sometimes seen in connection with gonorrhœa without apparent complications is, in some instances at least, evidence of a true gonorrhœal septicæmia.

2. A true gonorrhœal septicæmia in cases in which there is no evidence of local complications may run a course not dissimilar to that of typhoid fever.

3. In doubtful cases of continued fever associated with gonorrhœa the possibility of a gonorrhœal septicæmia should always be borne in mind.

* * *

CASES OF ULCERATIVE ENDOCARDITIS FOLLOWING GONORRHŒA.

A. Two Instances of Pure Gonorrhœal Endocarditis with Autopsy.

CASE II.—*Male, aged twenty-one years; gonorrhœa; septicæmia; ulcerative endocarditis of the aortic valve with Flint murmur; death; autopsy.*

Hospital No. 48,901; Medical No. 17,794. C. L., colored, male, aged twenty-one years, cart driver, entered the Johns Hopkins Hospital on 14th November, 1904, complaining of a cold, shortness of breath, and cough.

Family History. Parents living and well. One brother and one sister, living and well. No family history of tuberculosis.

Previous History. Patient has always been strong and well. Denies acute infections including venereal disease. Neither drinks nor smokes. Has always done manual labor. Has been married sixteen months; wife is well.

Present Illness. Three weeks prior to entry he was exposed to a rain storm, working all day in his wet clothes and suffering from chilly sensations. On the following day he had a "cold" and a slight hacking cough for which he took medicine for two weeks without benefit. By the end of the second week (6th November) he noticed shortness of breath after coughing and on exertion,

particularly on walking fast or going up stairs. There was considerable expectoration of "phlegm." On the morning of admission he noticed, for the first time, œdema of his feet and legs. There has been nausea and vomiting on several occasions. On the day of entry the following note was made by the house physician, Dr. Giffen: "The patient is a very well developed young man. Pupils are equal; tongue slightly coated; mucous membranes of good color. Superficial glands of the neck are palpable but not markedly enlarged. There is marked sclerosis of the veins of the arm.

"The thorax is well formed; angle wide; expansion equal. Vocal fremitus diminished over the left upper lobe; percussion clear throughout. Crackling râles are heard just above and below the right clavicle, as well as a few in the upper part of the right interscapular space and at both apices.

"*Heart.* Point of maximum impulse in the sixth interspace, 8 cm. from the midsternal line. Relative dulness extends 10 cm. to the left at the apex, 4 cm. to the right of the median line. Pulsation in the temporal artery is visible; presystolic venous wave in the neck; slight precordial pulsation. On palpation there is an impulse with both systole and diastole. The pulse is definitely collapsing, of small volume and pressure, 28 to the quarter. The vessel wall is sclerotic. On auscultation at the apex there is a resonant, rumbling diastolic murmur followed by a sharp first sound. The second sound is indistinct. At the base there is a rough diastolic, heard in the second right interspace, loudest in the third left interspace. The two sounds are very sharp and snapping, the pulmonic much accentuated. A diastolic murmur is heard over the body of the heart.

"The abdomen is slightly full. Relative hepatic dulness begins at the sixth right rib and extends three fingers' breadth below the costal margin in the mammillary line. The spleen is not palpable. There is œdema of the feet and slight œdema of the legs; genitalia normal."

Blood. Red blood corpuscles, 4,480,000 to the cubic millimetre; colorless corpuscles, 9700 to the cubic millimetre; hæmoglobin, 90 per cent.

The temperature, which, on entrance, was 98.6° fell by 8 P.M. to 98.2° and to 95.6° at 8 the following morning. At noon on 16th November it was 96.2°.

16*th November.* At 9 o'clock the following note was made by Dr. Thayer: "The patient is propped up in bed. There is well marked throbbing of the carotids. The tongue has a white coat. The pulse is regular, 27 to the quarter, of moderate size, abrupt, suggestive of a Corrigan pulse, though by no means typical."

"Thorax, symmetrical; costal angle of about 90°; precordial region a little fuller than on the right side. Point of maximum impulse visible in the sixth interspace 9.7 cm. from the midsternal line. Impulse, not particularly strong. Relative dulness extends just beyond the point of maximum impulse and 3.8 cm. to the right of the midsternal line. The maximum diameter of the area of dulness is 15.5 cm. At the apex there is a distinct thrill felt best in

the sixth interspace inside the point of maximum impulse and leading up to the impulse. At the apex a rumbling, presystolic murmur is heard ending in the first sound which, though feeble, is abrupt. The second sound is replaced by a soft, distinct, diastolic murmur. Immediately above and outside the impulse the diastolic murmur becomes more audible, and in the axilla, where the presystolic murmur has wholly disappeared, a dull humming first sound and a loud diastolic murmur are clearly heard. Passing inward in the sixth space the first sound becomes louder and the rumble is distinct; the diastolic murmur is feeble. Above the sixth rib, within the parasternal line, the presystolic murmur disappears and there is heard a fairly sharp first sound and a distinct second sound with a loud aortic diastolic murmur. In the second and third left interspaces the first sound is dull and humming, the second sound intensely accentuated. In the second right interspace there is a faint systolic and a distinct diastolic murmur. An element of the second sound is, however, heard. The diastolic murmur is best heard in the fourth left interspace. In the carotids there is a faint systolic hum; in the femorals, a distinct, short systolic tone.[1]

"*Lungs.* There are still a few râles at both apices and an explosion of fine rales on slight cough at the right apex. When propped up in bed the liver is not palpable. By percussion, it extends apparently just below the costal margin in the mammillary line."

Examination of the fresh blood shows no malarial parasites. Leucocytes, 24,000 to the cubic millimetre.

18*th November.* The temperature which was normal on the morning of the 16th, rose in the afternoon to 102° and fell again to a subnormal point by the following noon, rising, however, again in the afternoon. On the morning of the 18th it was 95.7°; by noon, 102.2°. A note made shortly after this by Dr. Cole, states that the patient was very ill; respirations 10 to the quarter; pulse 28 to the quarter, forcible, of large volume—a typical Corrigan pulse. The cardiac impulse was 10 cm. from the midsternal line. There was a slight presystolic thrill. The shock of both sounds was well felt. The first sound at the apex was loud and snapping and followed by a very short systolic murmur. It was preceded by a very loud rumble heard throughout almost the whole of diastole and running into the first sound. This disappeared as one passed outward, and a soft, blowing, diastolic murmur was heard throughout the whole period. Over the body of the heart both sounds were loud and booming. A soft to-and-fro murmur was heard along the left sternal margin, the diastolic being louder than the systolic. Along the right sternal margin, at the base of the heart, these murmurs were superficial, and over the sternum at the level of the second intercostal space, there was a scratching sound almost suggestive of friction. In the first and second right and left interspaces and over the

[1] Ventricular systole.

subclavians there was a rather coarse systolic murmur differing in quality from that heard elsewhere. Leucocytes, 22,500 to the cubic millimetre.

19*th November*. The intermittent fever still continued. The following note was made by Dr. Thayer: "The patient looks very ill, the face is puffy, the pulse larger than formerly, 21 to the quarter, definitely collapsing; there is no great change in the position of the apex impulse.

"*Heart*. The first sound is fairly sharp, and the diastolic murmur is succeeded by a long rumble followed by a slight first sound. As one passes above the fourth rib there is a slight systolic and diastolic murmur associated with an intensely accentuated second sound, most marked in the third left space. The diastolic murmur is loudest at the fourth cartilage. In the aortic area there is a short to-and-fro murmur. The dulness extends 4 cm. to the right of the midsternal line."

The irregular temperature still continued and two days later, on the 21st, it was noted by Dr. Thayer that the pulse seemed larger than formerly. "A little inside the nipple the first sound is rather abrupt and loud and the mid-diastolic rumble particularly intense. At the parasternal line the mid-diastolic rumble becomes feeble, the second sound sharper, and the soft early diastolic more audible. The accentuation of the second pulmonic sound is extraordinary." A tracing from the radial pulse was suggestive of aortic insufficiency, the pulse at this time being 36 to the minute and the maximum pressure (Riva-Rocci, narrow band) 103 mm.

Irregular, intermittent fever still continued, the temperature ranging between 97° and 103°. On the 23d the following note was made by Dr. Thayer: "The pulse is much larger than formerly and definitely collapsing. The point of maximum impulse is in the sixth space, 10.8 cm. from the midsternal line. There is a well marked thrill at the apex which is associated with the impulse, whether diastolic or systolic, it is difficult to tell by palpation. The rumble is clearly presystolic. The first sound is very feeble. Inside the apex there is a rumble leading up to a fairly sharp first sound. As one passes inward a soft systolic murmur becomes audible in addition to the diastolic. There is a to-and-fro murmur in the aortic area and along the left sternal border. The vessels of the neck pulsate markedly. The patient was distinctly losing ground."

On examination of the urethra a purulent discharge was discovered, the smears showing many pus cells and a moderate number of intracellular diplococci decolorizing by the method of Gram.

On the following day Dr. Cole noted that the patient was much worse. The respirations were 64, gasping; pulse 30 to the quarter, of Corrigan quality; marked throbbing of the vessels of the neck. The resonance over the left front was impaired, numerous medium and coarse râles being audible, while at the apex, the breath sounds were harsh with many fine crackling râles and prolonged expiration. High up in the axilla the breath sounds were tubular, and numerous coarse râles were heard in both backs. There was no

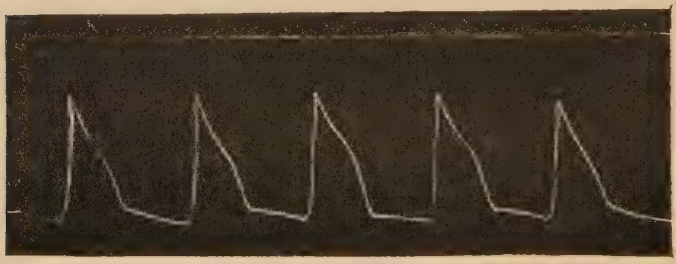
great change in the cardiac signs. During the day the patient became very noisy and the pulse was extremely rapid. In the evening stupor came on, followed by death at half-past 1 in the morning of 25th November.

The *urine* was free from albumin throughout, the specific gravity varying from 1012 to 1025. There were, however, occasional hyaline and granular casts and a varying number of leucocytes in the sediment.

The blood pressure, taken by the Riva-Rocci apparatus with the old, narrow band, was extremely low, the records ranging from 110 to 96 on the day of death.

On 18th and 21st November cultures were taken from the circulating blood. On the first occasion, 7 c.c. of blood were distributed upon one plate and two flasks. On the second occasion 20 c.c. of blood were distributed among three plates and three flasks. The cultures were negative.

FIG. 2



CASE II.—Radial pulse, 21st November, 1904.

In view of the discovery of the urethritis the diagnosis was gonorrhœal endocarditis. The remarkable accentuation of the second pulmonic sound, together with the loud, rumbling presystolic murmur and the rather abrupt first sound led us to a diagnosis of a combined mitral and aortic lesion. The necropsy, however, revealed a pure aortic endocarditis.

Necropsy (No. 2424) by Dr. MacCallum, nine hours after death.

Anatomical diagnosis: Acute vegetative and ulcerative endocarditis; bronchopneumonia; œdema of the lungs; parenchymatous degeneration of the kidneys; infarctions in the kidneys and papillary muscles of the heart; cardiac hypertrophy and dilatation; epicardial fibroid nodules; beginning arterio-sclerosis; ecchymoses in the mucosa of the bladder.

The *heart* is greatly enlarged; the enlargement of the left ventricle being especially prominent. The arteries are covered with complete chains of epicardial nodules. There is a thick, irregular, tendinous patch over the front of the right ventricle. The surface of the heart is, in general, smooth except for the epicardial nodules. The fat over the heart is gelatinous and dark yellow. The apex of the left ventricle projects at least 3 cm. beyond that

of the right and constitutes the point of the heart. The right auricle is distended with post mortem clot. Its lining is smooth. The auricular appendage also contains a post mortem clot. The tricuspid and pulmonic valves are normal in appearance. The blood clot is very firm and makes a perfectly distinct mould of the valve. The mitral valve is normal in appearance. The chordæ tendineæ are delicate. The papillary muscles of the anterior leaflet show, however, an opaque patch of yellowish color bounded by a zone of dark red. On section this appears to be a necrotic, coagulated area surrounded by a zone of hemorrhage. On opening the aorta it is found that the edges of the valves are all delicate. The right coronary segment and the middle segment are normal throughout. The left coronary segment, however, has suffered a great change. The edge of the valve throughout is quite delicate. The base of the valve, however, is covered with large vegetations, and an extensive erosion of the tissue has taken place, so that the whole floor of the sinus of Valsalva is destroyed and the scissors can be passed from the left ventricle into the aorta through the open floor of the left coronary sinus of Valsalva. The valve thus remains as a bridge across the aorta from the lower edge of which there hang large irregular vegetations. The sinus is covered everywhere by rough vegetations. The remains of its floor project outward and are roughened in the same way. The sinus has been extended by ulceration into the wall of the left ventricle, especially anteriorly and toward the left where a cavity has been hollowed out in the upper portion of the wall of the left ventricle just behind the anterior mitral segment. The chief mass of vegetation which hangs in the blood stream and is covered with blood clot, measures about 18 mm. in length. It is soft and friable and has a folded, irregular, yellow surface. The post mortem clot may be pulled off from it like a glove finger leaving it quite clean and uniformly grayish yellow. The apices of all of the mitral papillary muscles are crowned by areas of necrosis. The heart muscle is fairly firm and the wall of the left ventricle measures about 2 cm. in thickness. On tangential section the muscle is very opaque and much mottled with pale grayish and dark red areas. The coronary arteries show no marked sclerosis. There is a uniform roughening of the intima, especially in those areas where the epicardial nodules have developed. The endocardium is elsewhere smooth. That of the left ventricle has spots of opacity shining through. The right ventricle measures about 4.5 mm. in thickness and about 8.5 cm. in length. The left ventricle measures 9.5 cm. in length. The aorta shows streaks of sclerosis not very far advanced.

Lungs. There is a small amount of fluid in the left pleura. On removing the left lung it is found to be non-adherent. The surface of the lung is slightly roughened by a few tags representing old adhesions. The pleural surface is everywhere smooth and glistening, but very opaque and grayish as if the pleura were greatly thickened. The apical portion of the lung is inflated and soft. The remainder of the upper lobe and the whole of the lower lobe are very

heavy and firm to the touch. Along the edges of the lobes, particularly along the edge of the lower lobe there are numerous small pin-head sized nodules, which are grayish and somewhat translucent. These seem to be solid masses, and not merely air bubbles. The lymph glands at the hilum are somewhat enlarged. They are soft, reddened and very œdematous. The bronchi contain a certain quantity of frothy fluid and their walls are smooth. On section the lung is very firm. The upper portion of the upper lobe is evidently air-containing. The lower portion of the upper lobe is quite smooth on section, of a grayish red color with abundant areas of darker gray or black pigmentation, and the tissue is relatively airless. The same condition is found throughout the lower lobe but not quite so uniformly, there being patches of air-containing lung scattered here and there. The consolidation involves, irregularly, the whole lower portion of the upper lobe and the whole of the lower lobe with the exception of the small scattered air-containing spaces or areas described. The right lung is quite densely adherent over the upper lobe; it is rather smaller than the left and is very much roughened over the upper and middle lobes by adhesions. There is a deep scar causing a depression in the upper lobe. The middle lobe is densely adherent to the upper lobe and also to the lower. The anterior portions of the lung are air-containing and crepitant. The posterior and lower portions of the middle lobe feel solid. The whole posterior portions of both the upper and lower lobes feel firm. The bronchi contain a blackish, frothy fluid. On section, the same type of smooth elastic consolidation is seen throughout the upper and lower lobes as described in the left lung. Between the upper and middle lobe there is a mass of dense white scar tissue which occludes the bronchi and vessels. The posterior part of the lung is very œdematous and very elastic and firm, dark, reddish gray in color and almost entirely airless. The cut surface is quite smooth. A bit of the lung just floats in water.

The *spleen* measures 14 x 9 x 6 cm.; weight, 200 gm. The capsule is roughened by old adhesions. On section the splenic pulp is somewhat swollen. The Malpighian bodies are very large and prominent, opaque, grayish white in color. The *stomach* and *duodenum* and *pancreas* are not remarkable. The *liver* measures 29 x 19 x 13 cm. and weighs 2450 gm. Its capsule is smooth and uniform in appearance. On section the lobulation of the liver is very distinct. The lobules are extremely large and have a yellowish-gray periphery and a reddish centre. The red portion is very sharply marked off from the grayer portion and frequently shows central points of orange yellow.

Kidneys. The left kidney is firm and not enlarged, measuring 11 x 6 x 5 cm. The capsule splits in peeling off and leaves a rather smooth surface which is of a grayish red color. On the surface in the middle line there appears a small opaque area surrounded by a dark red area. On section this opacity extends 4 mm. into the substance of the kidney and is surrounded completely by a zone of hæmorrhage. The cortex of the kidney is thick, measuring 12 mm.

The striations are straight. The glomeruli are prominent. The epithelial portions of the cortex are rather opaque and gray. The right kidney presents no opacities on the surface. The capsule strips off smoothly. On section it presents the same general appearance as the left, the cortex being swollen and the glomeruli particularly prominent. The kidneys weigh 450 gm. together. The *adrenals* are apparently normal. The *cervical lymph glands* are much enlarged, very œdematous and dark red. The *thyroids* and *œsophagus* are not remarkable.

Bladder. The mucosa of the bladder is smooth. There are some ecchymoses at the fundus. The *urethra* is quite normal in appearance. The *testicles* and *epididymes* are normal in appearance.

Bacteriological Report by W. W. Waite. Cover-slip preparations were made from vegetations on the aortic valve and from the urethra. Plate cultures on ordinary media were made from the pericardial cavity, heart's blood, vegetations on the aortic valve, gall-bladder, liver, spleen and kidney. Rabbit's blood agar tubes were made from vegetations on the aortic valve.

Cover-slip preparations from the urethra stained with methylene blue showed several kinds of organisms. That present in greatest numbers was a diplococcus of a distinct biscuit-shape, which was inside and about pus cells. The cover-slip preparations from the vegetations showed in any single field numbers of organisms which were all cocci arranged singly and in pairs. The paired organisms had their long axes parallel and were distinctly biscuit-shaped. None of the organisms held their stain when treated by Gram's method.

On the rabbit's blood agar tubes from the vegetations there were numerous small translucent colonies which appeared to be all of one kind. A gentian violet stain showed but one type of organism which was a diplococcus arranged singly and in pairs, which decolorized completely by Gram's method. Transfers were made to blood serum, plain slant agar and hydrocele agar. The blood serum and agar showed no growth. The hydrocele agar, however, contained many small clear translucent colonies on the surface of the medium. A culture allowed to grow twenty-four hours in the incubator at 36° C. and then kept at room temperature lived only two days.

Diagnosis: *micrococcus gonorrhœæ.*

The plates on ordinary media contained a few colonies of micrococcus roseus and micrococcus cereus. These were probably air contaminations or end infections. The heart plates contained a few colonies, the pericardium, 1; vegetations, 2; gall-bladder, 4; liver, 6; spleen, 22.

CASE III.—*Male; aged forty-two years; gonorrhœa; arthritis; septicæmia; ulcerative aortic endocarditis; death.*

Hospital No. 49,214; Medical No. 17,889. R. W., aged forty-two years, married, a dyer by trade, was admitted to the Johns Hopkins Hospital on 12th December, 1904.

Family History. Father, living and well. Mother, died at fifty-two of typhoid fever. Two brothers, living and well. Three brothers died in infancy. One sister, living and well; two died of unknown cause. Family history, otherwise good.

Previous History. Has always been a healthy man. Had a severe attack of scarlet fever at five, since when he has been bald. Measles at seventeen; whooping-cough at seventeen. No other serious illnesses. Seven years ago he suffered from "indigestion" for six months, but has had no trouble since then. Denies lues.

Habits. Drinks an occasional glass of beer; smokes one package of tobacco a week. Average weight, 148 pounds.

Present Illness. Four weeks ago developed an acute gonorrhœal urethritis. Two weeks ago noticed that his right wrist was tender and lame, so much so that he was obliged to stop work on the following day; it has been gradually growing stiffer and more painful. Three days ago his right shoulder became lame and for two days his right eye has been a little sore early in the morning. There has been no trouble with vision. Has not slept well for the last four nights, and for the last two nights there has been profuse sweating. There has been no cough; no expectoration.

On entrance it was noted that the patient was well nourished; tongue fairly clean; mucous membranes of good color. Slight conjunctivitis of the right eye. The pupils were unequal, the left the larger. Both reacted to light and accommodation. There was marked pulsation of the vessels of the neck and of the brachials. The skin was hot and dry. The lungs were clear throughout.

Heart. Point of maximum impulse in the fifth interspace 9.5 cm. to the left of the median line. Relative cardiac dulness begins at the upper border of the third rib, extending, in the fourth interspace, 2.5 cm. to the right and 9.5 cm. to the left. All over the heart is heard a soft, systolic bruit. Sounds otherwise clear. The second pulmonic is not accentuated, though there is a reduplication of the second sound in this area. Pulse, 21 to the quarter, regular in force and rhythm, volume good, tension good, vessel wall not felt. Blood pressure (Riva-Rocci, broad band), 125 mm. Abdomen natural, no tenderness. Neither spleen nor liver palpable.

Genitalia. Slight œdema with glairiness of the meatus. There was a small accessory meatus with a slightly glairy discharge as well. Gonococci were demonstrated in the discharge. No swelling of the epididymis.

Joints. Right wrist thickened, hotter than the other wrist, not especially painful nor tender, slightly reddened. Motion limited in all directions. Pain and limitation of motion in the carpo-metacarpal joints of the thumb. Other joints appear to be free.

Examination of the blood showed that the red corpuscles were regular in outline, of good shape and size. There was a slight leucocytosis but no parasites.

Blood Count. Red blood corpuscles, 4,960,000 to the cubic millimetre; colorless corpuscles, 10,600 to the cubic millimetre; hæmoglobin (Gowers), 98 per cent.

13*th December.* The temperature, 99° on admission, fell to 98° at 8 P.M. and was normal on the following morning. Note by Dr. Cole: "Slight injection of the conjunctiva; no purulent discharge; no opacity of the cornea; pupils equal; no glandular enlargement excepting for two glands about as large as peas in the left axilla, and the right epitrochlear gland, which is about the size of a pea. The left epitrochlear is just felt. Chest, well formed; lungs everywhere hyperresonant on percussion. Breath sounds distinct. A few piping rales.

"*Heart.* Point of maximum impulse not well seen nor felt. No absolute cardiac dulness. Relative cardiac dulness extends 8.5 cm. to the left; above to the third rib. Slight reduplication of the second sound at the apex. Soft systolic murmur in the pulmonic area. Aortic and pulmonic seconds of normal intensity. Spleen not palpable.

"*Joints.* Complains of tenderness in the right shoulder. There is no swelling, no heat. The right wrist is swollen for the most part on its inner surface; temperature, elevated; moderate tenderness and swelling being most marked on the radial side of the dorsum of the wrist and about the head of the radius; do not extend up the sheaths of the tendons. No other joints affected."

16*th December.* The temperature remains normal. No great change in the symptoms. Dr. Osler noted on this date that there was a well marked systolic murmur.

18*th December.* Dr. Cole observed on this date that the right wrist was swollen, especially over the inner portion, the skin red and hot. The patient complained of throbbing pain in the joint, worse at night. The pain was sufficient to awaken him. There was no restriction of motion in the right shoulder; no tenderness. There was an appearance of atrophy of the interossei on the dorsum of the right hand. The motion of the wrist was restricted. There was œdema about the joint, which extended about one-third of the distance up the arm.

"19*th December.* Red blood corpuscles, 5,122,000 to the cubic millimetre; colorless corpuscles, 10,400 to the cubic millimetre; hæmoglobin (Gowers), 97 per cent.

"Urethral discharge still shows diplococci, which decolorize by Gram. The pain in the wrist continues. The swelling now extends half way up the arm, the redness and tenderness being most marked about two and one-half inches above the wrist, where there is a brawny œdema, the skin being red and hot. The wrist is stiff but not extremely tender. The heart sounds are quite clear (Cole)."

3*d January,* 1905. The patient has been in the hospital since 12th December and has had at intervals a small amount of fever reaching above 100°. For

the past five days the temperature has been lower than usual. Yesterday morning it rose to 99.5°. The patient was out of bed at this time and complained only of a slight headache. This morning he arose as usual, feeling well, but was not especially hungry. At 8 A.M. the temperature was found to be 100.5° and the patient was at once put to bed. The temperature steadily rose to 103.8° at 4 P.M. On examination, the tongue was found to be dry and red, but not coated. The pulse was 120; the lungs were clear throughout on auscultation and percussion. There was a soft, blowing systolic murmur heard, especially, along the left sternal border. The abdomen showed nothing remarkable. The spleen was not palpable. The patient complained of feeling drowsy and sleepy. Colorless corpuscles, 16,500.

On the succeeding day (4th January) Dr. Cole made the following note: "With a sudden rise of temperature which occurred yesterday there have been no symptoms excepting that the patient has complained of slight chilly sensations. The face is a little flushed, the tongue moderately coated and dry. The pharynx is red and injected though the patient complains of no soreness. Scattered over the abdomen, back, lower chest and also, to a lesser extent, on the arms, are small elevated red spots which disappear on pressure, and resemble somewhat rose spots except for their size which is 5 to 6 mm. in diameter. They are a little more elevated and surrounded by a zone of slight hyperæmia. The patient thinks that he has previously noticed such an eruption over the body. Respiration, quiet and slow; lungs, quite clear throughout on percussion and auscultation.

"*Heart.* Point of maximum impulse not seen nor felt. Relative cardiac dulness difficult to outline; extends apparently 9 cm. to the left at the fifth rib, to the upper border of the third rib above, and 2.5 cm. to the right at the fourth interspace. No impulse is to be felt anywhere over the cardiac area. At the apex both sounds are well heard, the second almost as loudly as the first, while the systolic and diastolic pauses are of almost equal length. The heart's action is not rapid and is regular. No murmur can be heard at the apex or over the body of the heart. Both second sounds at the base are snapping, the aortic second being louder than the pulmonic. Over the sternum and in the second and third left interspaces near the costal margin, the second sound is a little prolonged and, though no definite murmur can be made out, it may be that a faint diastolic souffle is present. The abdomen is full; neither tender nor distended. The spleen cannot be felt. The edge of the liver is palpable one finger's breadth below the costal margin in the mammillary line. The right wrist is still stiff. The patient also complains of tenderness in the left wrist, though no swelling or redness is to be seen." Cultures were taken on this date from the blood. 20 c.c. of blood were distributed on two plates of hydrocele fluid agar; four plates of plain agar; one flask of bouillon; one flask of litmus milk.

On the following day the colorless corpuscles were 8000 to the cubic milli-

metre. Blood pressure, 116 mm. The temperature was lower—not above 100°.

6th January. The sputum, small in amount, mucopurulent and tenacious, showed microscopically leucocytes and epithelial cells; it was negative for tubercle bacilli. The blood pressure at 5.50 P.M. was 135 mm.

There was no growth in the cultures made on 4th January.

7th January. The temperature on the 6th ranged between 100.2° and 102.5°. On the 7th it fell gradually to 99.6° at 8 P.M. Colorless corpuscles, 18,900 to the cubic millimetre.

9th January. On this date, Dr. Cole noted that the patient's temperature was lower; pulse 23 to the quarter, regular. There was pain and tenderness over the left side of the larynx; no swelling or redness. The eruption of

FIG. 3

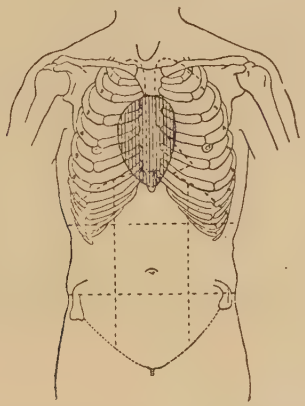


Chart showing area over which the diastolic murmur was heard on 10th January, 1905. (Dr. Cole.)

reddish papules over the body had disappeared to a certain extent. The spleen could not be felt. The œdema and tenderness of the right wrist had almost entirely disappeared, but there was still some stiffness. The patient complained of a slight aching in his ankles.

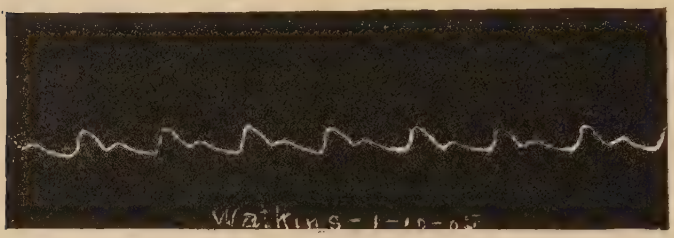
Blood Count. Red blood corpuscles, 5,252,000 to the cubic millimetre; colorless corpuscles, 11,360 to the cubic millimetre; hæmoglobin (Gowers), 82 per cent.

On the following day (10th January) Dr. Cole noted that the papular eruption was disappearing; pulse, 26 to the quarter, regular, of rather large volume with a forcible quick impulse and a slightly collapsing quality.

The impulse of the heart was neither seen nor felt. Sounds, best heard in the fifth space 8.5 cm. from the midsternal line, to which point the relative cardiac dulness extended; to the right it reached 4 cm. in the fourth interspace,

and above to the upper margin of the third rib. There was no shock to be felt at the apex or base. At the apex the heart sounds were quite clear, both being well heard. The second was rather loud. Passing upward and inward in the fourth interspace, a soft, prolonged, blowing diastolic murmur became audible; this was heard over rather a wide area as shown in the diagram. Its maximum intensity was over the middle of the sternum, opposite the fourth interspace. The pulmonic second sound was not accentuated but was loud and well heard. The aortic second was also well heard but was not as loud as the pulmonic. There was no systolic murmur at the base.

FIG. 4



CASE III.—Radial pulse, 10th January, 1905.

11*th January.* Yesterday evening the patient began to complain of sharp abdominal pain which could not be definitely localized and was relieved by movements of the bowels. Colorless corpuscles, 15,400 to the cubic millimetre.

Cultures were again taken from the blood; 20 c.c. of blood were taken from the median basilic vein under antiseptic precautions and divided among six plates of agar, one plate of litmus milk and one flask of bouillon.

13*th January.* At the morning visit Dr. Osler made the following note: "The patient looks pale, the tongue is red and fissured; pulse is full, soft, dicrotic. The skin is clear; no petechiæ.

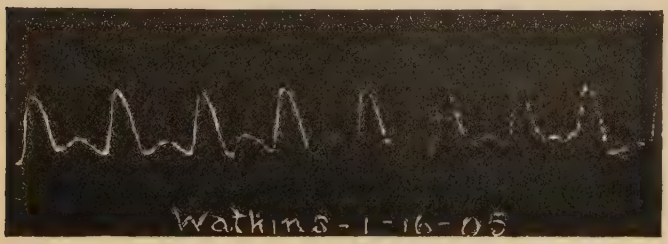
"*Heart.* Apex beat not visible; no marked pulsation in the vessels of the neck. There is a wavy impulse in the veins of the arm. In addition to the distinct pulsation there is a filling of the vein with expiration and the partial emptying with inspiration. There is no shock of either sound at apex or base; no forcible impulse; no especial impulse in the cardiac area. On auscultation, at the apex both sounds are heard. There is a soft murmur with the first sound. Toward the base and along the left sternal border there is a diastolic murmur which increases in intensity and is at its maximum in the second left space; it is well heard also at the second right costal cartilage and over the manubrium; well heard down the sternum. The pulse has become of a collapsing quality."

On the following day (14th January) Dr. Osler noted that the apex beat was faintly visible in the fifth left interspace inside the mammillary line; not

palpable. The shock of neither sound was palpable. No thrill at the base. A wavy impulse in the neck but not of the character of aortic insufficiency. "Visible pulsation in the upper arm is quite marked. Radial pulse has become collapsing. At the apex both sounds distinct, somewhat increasing in intensity toward the sternum. No systolic heard at the apex. Sounds quite loud at the lower sternum. On approaching the third rib there is a diastolic murmur of great intensity, which, to-day, has definitely changed in quality. It is not only more intense but has a decidedly musical sound. It is heard well also at the aortic cartilage."

Results of cultures taken on 11th January. On the plates containing equal quantities of agar and blood there was in twenty-four hours, at 37° C., a growth of faint grayish translucent colonies, deep in the medium; all flat and round—not oval. On blood agar, surface smears, there was a good, discrete growth of fine grayish translucent colonies. On hydrocele agar there was a growth of discrete, grayish, translucent colonies.

FIG. 5



CASE III.—Radial pulse, 16th January, 1905.

These colonies all consisted of a biscuit-shaped diplococcus without motility, staining readily and evenly and decolorizing by Gram's method.

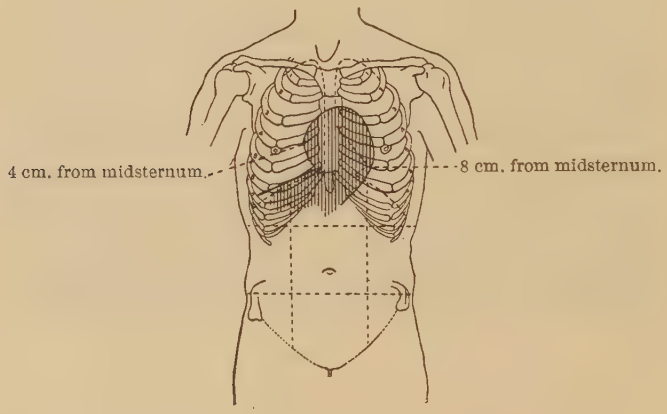
After forty-eight hours there was no growth on the surface of the plates of blood and agar. The colonies already present were 1 to 2 mm. in diameter—no subsequent increase in size. On the blood agar surface smears the colonies in forty-eight hours were not over 2 mm. in diameter. On blood serum in forty-eight hours there were faint discrete colonies. On hydrocele agar, in forty-eight hours, the colonies were slightly larger—some fusing of the colonies. There was no growth on plain agar slant, on hydrocele fluid and bouillon or on litmus milk. Diagnosis: *Gonococcus.*

On the following day (16th January) Dr. Cole noted that the area of cardiac dulness reached 2.5 cm. to the left of the midsternal line and 4 cm. to the right in the fourth interspace. The spleen was not to be felt.

17th January. Blood Count. Red blood corpuscles, 4,640,000 to the cubic millimetre; colorless corpuscles, 14,800 to the cubic millimetre; hæmoglobin, 82 per cent.

The patient steadily lost ground. On the 18th he complained of epigastric pain and had several attacks of nausea and vomiting. On this date the following note was made by Dr. Thayer: The patient looks rather pale and ill, the tongue is very red and beefy; pulse, regular, of large size, short duration, ill sustained, 25 to the quarter. There is moderate heaving in the precordial area. Apex impulse, not clearly defined. The cardiac dulness begins above at the upper border of the third rib and extends about 4 cm. to the right of the midsternal line and, over the fifth rib, about 8 cm. to the left. The greatest diagonal dulness from left to right measures a trifle over 13 cm. The sounds are best heard in the fifth interspace just inside the outermost dulness. At the apex the first sound is clear, the second followed by a soft, blowing diastolic murmur which is prolonged through the greater part of diastole, and, in the

FIG. 6



CASE III.—Showing cardiac dulness on 18th January, 1905.

fourth space at about the parasternal line, becomes louder and more accentuated in the latter part of diastole, taking on the features of a mitral presystolic murmur. Along the left border of the sternum the first sound is clear, the second, replaced by a well-marked diastolic murmur which is heard loudly in both aortic and pulmonic areas. The element of the second sound is louder in the pulmonic than in the aortic area. The murmur is well heard over the manubrium. In the carotids there is only a rather faint systolic tone; slight tone in the femorals. It is rather striking that the presystolic murmur is so well heard inside the parasternal line, as well as in the tricuspid area.

The nausea and vomiting continued. On the 20th Dr. Osler noted that the murmur had increased greatly in volume and intensity. No systolic murmur was audible.

On the 21st I saw the patient again, noting that the pulse was markedly dicrotic, ill-sustained, though not of a particularly large size nor of a characteristic aortic character. "At the apex but two sounds are heard; a long and rather rumbling murmur with a short sound of moderate intensity. The short sound is the first sound. The long rumbling murmur occupies, apparently, all diastole. Passing inward, the diastolic murmur becomes greatly increased in intensity, loudest at the sternal end of the fourth left interspace, where the first sound is barely audible, the loud roaring murmur being almost the only sound. In the second left interspace the second sound is fairly sharp and the murmur is of less intensity. In the aortic area there is a to-and-fro murmur of moderate intensity. An element of the second sound is heard. It is interesting that, at the apex, the murmur, though feebler than near the sternum, runs directly into the first sound. Near the sternum it reaches its climax and comes to an end a little earlier. The right side is much enlarged, reaching, on percussion, as much as 6 cm. to the right of the midsternal line. The dulness on the left reaches about 9.2 cm. outward over the fifth rib. There is a slight femoral tone. The liver flatness reaches 7 cm. below the tip of the ensiform and 4 cm. below the costal margin in the mammillary line."

On 23d January, Dr. Osler noted a distinct, slight vibratory thrill, and on the following day Dr. Cole described a well marked thrill.

Blood Count. Red blood corpuscles, 4,108,000 to the cubic millimetre; colorless corpuscles, 13,200 to the cubic millimetre; hæmoglobin, 72 per cent.

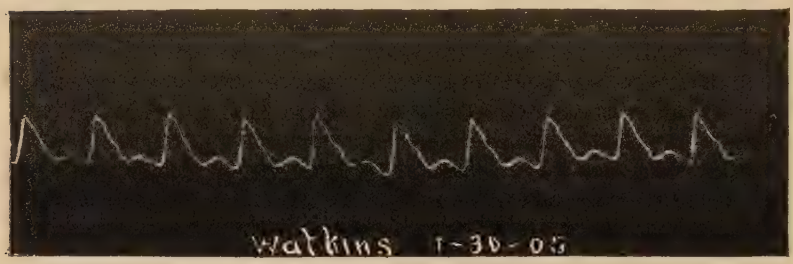
The temperature was very irregular, intermittent and remittent. Febrile paroxysms frequently accompanied with chills, occurred sometimes as often as three times in twenty-four hours.

On the 27th Dr. Thayer noted that the pulse was 30 to the quarter at the time of the visit; the right side of the heart extended on percussion about 5.8 cm. from the median line; on the left only about to the mammillary line or 10 cm. from the median line. The first sound was heard best in the fifth space a little inside the point of outermost dulness; it was not loud but was rather sharp; the second sound was immediately followed by a diastolic murmur which ran all the way up to the first sound, having, toward the end of diastole, something of a rumbling quality. In the fourth left interspace the murmur was louder and more like a mitral diastolic. It became still louder as one passed inward and was loudest a little outside of the left sternal border in the fourth space. The heart's action was so rapid that it was difficult to place the sound exactly, but at the point of greatest intensity of the diastolic murmur at the sternal and of the fourth space, the rumbling, loudest part of the murmur seemed to be late rather than early in diastole. At this point the first sound was very slight and the second barely audible, marking the beginning of the murmur. In the pulmonic area, in the second left interspace, there was a soft to-and-fro murmur in association with the two sounds, the second, sharply accentuated. The same is true in the aortic area, the murmurs,

however, being rather louder. The second aortic sound is sharp. There is no sharp tone in the aorta; a tone in the crurals of moderate intensity. "The striking features of this case are an extremely large right side with auscultatory signs which would point to a pure aortic lesion. On the other hand, the first sound at the apex has a rather short and abrupt character which might suggest mitral disease. The position of greatest intensity of the late diastolic murmur in the tricuspid area is again remarkable. Over the right side of the chest and the dull area to the right of the sternum the heart sounds are well heard, each followed by a soft murmur. At the end of the third left interspace the diastolic murmur is limited to early diastole, while over the whole of the rest of the left precordial area there is a late diastolic accentuation. The pulse is collapsing and of aortic quality."

The patient steadily lost ground; there was intermittent fever with frequent chills. Examination of the fresh blood on January 29th showed that the red blood corpuscles were of normal size; a little pale; no malarial parasites. There was a moderate leucocytosis with a moderate increase in polymorphonuclears.

FIG. 7



CASE III.—Pulse tracing, 30th January, 1905.

30*th January.* Dr. Osler observed on this date, that "the most interesting change that has occurred is the rough diastolic over the body of the heart. Over the aortic area and along the left border of the sternum the murmur is soft, the maximum intensity being in the tricuspid area. There is a good deal of pulsation in the neck."

31*st January. Blood Count.* Red blood corpuscles, 3,164,000 to the cubic millimetre; colorless corpuscles, 25,000 to the cubic millimetre; hæmoglobin (Gowers), 60 per cent.

The patient steadily lost ground. On 2d February Dr. Cole noted that there had been no special change in the heart sounds excepting that the rumbling murmur in the fourth and fifth interspaces inside the parasternal line had become more marked and more typically presystolic in time, of entirely different quality from the diastolic murmur heard over the sternum and along the left sternal margin.

On 3d February Dr. Thayer noted that the patient looked puffy and doughy. There were a number of perfectly fresh petechial spots on the trunk and extremities. The pulse was 29 to the quarter, soft and of rather good size; of short duration; collapsing quality marked on raising the wrist. The pulsa-

FIG. 8

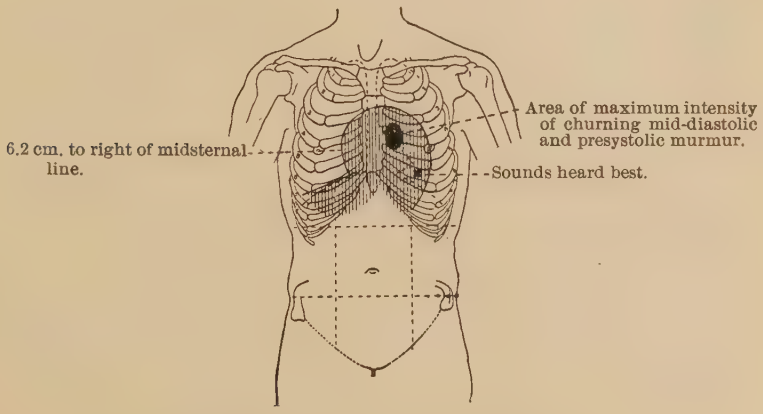
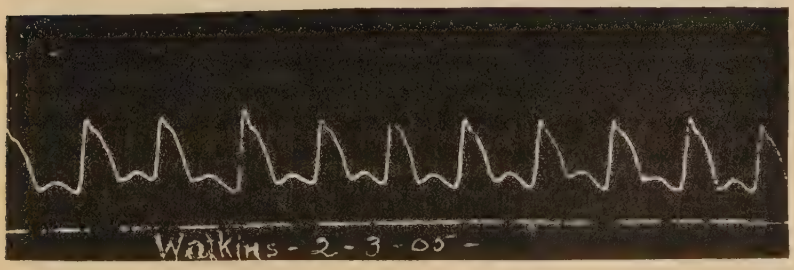

Area of maximum intensity of churning mid-diastolic and presystolic murmur.
6.2 cm. to right of midsternal line.
Sounds heard best.

Chart made by Dr. Thayer on 3d February, 1905.

tion of the carotids was fairly well marked. The apex impulse was not sharply localizable. Slight impulse just behind the left nipple. There was epigastric pulsation. On percussion the dulness extended 6.2 cm. to the right of the median line in the fourth space, and 5 cm. in the third. In the apex region

FIG. 9



CASE III.—Radial pulse, 3d February, 1905.

the sounds were best heard in the fifth space, about 7.5 cm. out. There was a gallop rhythm dependent upon a reduplication of the first sound or a very slight presystolic murmur, it was difficult to say which, as well as a very slight systolic murmur. The sounds were very soft and masked by loud

stertorous breathing. The second sound which was audible was followed by a very slight diastolic murmur. Passing inward a murmur became heard in diastole leading up to the first sound and beginning, apparently, immediately after the second sound. In the fourth space, inside the parasternal line, this became suddenly very loud and near the ear, of an echoing, vibratory quality and was almost the only sound heard. Listening very carefully a slight soft whiff of a different character might be heard at the beginning of diastole. Immediately above this the rumbling murmur disappeared and the first and second sounds were heard, followed by a soft diastolic murmur limited to the early part of diastole and of ordinary aortic quality. The second sound in the second left interspace was sharp and associated with this same diastolic murmur. In the second right interspace was heard a short systolic souffle and a fairly sharp second sound followed by a diastolic murmur. The churning mid-diastolic and presystolic murmur was heard with maximum intensity in the limited area marked on the chart in the third and fourth left interspaces. To the right of the sternum, in the dull area, the heart sounds were well heard—with a well marked to-and-fro systolic and diastolic murmur. These were especially loud in the third right space. There was a distinct pulsation in the dull area on the right.

The patient, who had been failing rapidly for a week and constantly complaining of feeling "awful sick," became weaker and more restless and died at 7.10 on the morning of 4th February.

The necropsy (No. 2463) was performed by Dr. MacCallum three and a half hours after death.

Anatomical Diagnosis: Acute aortic endocarditis with ulceration of the valves; acute splenic tumor with anæmic infarction; acute diffuse nephritis; myocardial degeneration; atelectasis and œdema of the lungs; slight cirrhosis of the liver; chronic adhesive pleuritis; diphtheritic cystitis.

"*Thorax.* The pleural cavity of the left side is free from adhesions but contains about 600 c.c. of turbid fluid, and the right pleural cavity is almost obliterated by thin veil-like adhesions. The pericardial cavity contains a little thick fluid. The surfaces are smooth and glistening. The heart is somewhat enlarged. The right ventricle is extremely flabby, and as the heart lies in the pericardium, a solid opaque mass can be felt through the walls of the right ventricle, projecting so as to be easily seen. It is apparently attached to the wall of the ventricle which cannot be lifted away from it.

"*Heart.* The heart is smooth externally and there is a small hæmorrhage over the anterior portion of the back of the ventricle. There is a similar small hæmorrhage on the posterior surface near the apex. The tricuspid valve, viewed from the auricle, shows no abnormality. The mass described above proves to be a papillary muscle. The tricuspid and pulmonic valves are quite normal. The mitral orifice measures about 3 cm. in transverse diameter. Viewed from the auricle no definite vegetations are seen. The valve is thick-

ened throughout its whole edge except for a small portion of the posterior valve. The posterior valve is much shortened. The thickening is most marked in the anterior leaflet, where it extends for a width of perhaps 7 mm. back from the edge. The chordæ tendineæ are practically normal. The aortic valves are covered on the ventricular side with a vegetation which involves the right and left coronary segments. The vegetations are large and rounded, measuring perhaps 1.5 cm. in diameter. They spring from the central portion of each of the valves and bind the two valves together so that the left coronary segment is much distorted and pulled over toward the right. A probe can be easily passed through the valves where the vegetations lie upon them, and thus into the ventricle.

"When the fresh clot is removed the vegetations are found to be very rough and irregular and covered with ridges. The holes in the valves are at least 6 mm. across. The valves are obviously eroded when viewed from the sinus of Valsalva, the eroded portion being roughened and covered with red clot. The left coronary artery shows some yellow plaques of sclerosis, but it is patent and wide. The right coronary artery is much smoother and shows no extensive plaques of sclerosis. The back of the mitral valve shows some yellow patches. The aorta is fairly smooth, there being some sclerosis and a thickening just above the valves. The myocardium of the right ventricle is excessively flabby. The wall of the ventricle measures 3 mm. in thickness. The myocardium of the left ventricle measures about 15 mm. in thickness; it is rather opaque and dull gray in appearance.

"The *spleen* measures 16 x 14 x 6 cm. and weighs 550 grams; it is very much enlarged. Its capsule is tense and dark grayish-red in color. The upper surface of the spleen shows two patches of dense, firm tissue which are slightly elevated above the surrounding surface and are grayish yellow in color with a margin of blackish red. Both of these areas are covered with a fibrinous exudate. On section they extend into the substance of the spleen and are opaque, grayish yellow in color. The larger is distinctly softened in the centre. The spleen is very much swollen and on section is rather grayish looking and opaque. The Malpighian bodies stand out sharply as opaque gray dots in an excessively hypertrophied splenic pulp.

"The *bladder* is distended with urine. In the posterior wall just below the fundus there are numerous red areas somewhat raised, dull on the surface, pale in appearance and surrounded by a margin of deep red spots. The mucosa of the bladder elsewhere is fairly normal, somewhat dull and granular at the trigone.

"The *prostate* is not enlarged but the prostatic veins contain, here and there, thrombi. The seminal vesicles are normal in appearance and contain a clear fluid. The testicles and epididymes are apparently normal."

Microscopically, the urethral mucosa was slightly infiltrated with leucocytes, while the mucosa of the bladder showed a typical diphtheritic inflammation.

Microscopical examination of the vegetations on the aortic valve showed a large number of diplococci of distinct biscuit-shape, most of which were intracellular. Some cells were packed full of cocci. The organisms decolorized by Gram's method.

Cultures on ordinary media from the heart and kidney were sterile. Those from the spleen showed one small colony of *streptococcus pyogenes;* from the abdominal cavity, one colony of *streptococcus pyogenes* and one of *micrococcus albus*. From the bladder which had been opened and somewhat exposed, a small bit of tissue was excised after singeing the surface, and put into the culture medium. Colonies of the *pseudodiphtheria bacillus* and *bacillus alcaligines* were obtained. Ascitic agar tubes were made from the vegetations on the aortic valve. On these there developed in pure culture, small, white colonies of biscuit-shaped diplococci arranged in tetrads and pairs which decolorized by Gram. No growth in milk. Diagnosis: *Micrococcus gonorrhœæ.*

At the same time Dr. Boggs made cultures from the heart's blood and from the vegetations on the aortic valve—smears on hydrocele agar. Those from the heart's blood were negative; those from the vegetations showed a pure culture of *micrococcus gonorrhœæ.*

This case was particularly interesting from the point of view of the physical signs. The remarkable presystolic accentuation of the diastolic murmur, the intensity of the presystolic rumble, the area in which it was heard, and the great extent of the dulness to the right would seem to have quite justified the suspicions which we had *intra vitam* of the existence of a combined aortic and tricuspid lesion. From the anatomical lesions, however, it would seem that this murmur must have been due to the disturbance caused by the regurgitation of a large mass of blood directly upon the anterior mitral curtain at the time of entry of the blood from the left auricle.

* * *

B. Four Cases of Ulcerative Endocarditis following Gonorrhœa.

CASE IV.—*Male, aged twenty-one years; gonorrhœa; arthritis; ulcerative endocarditis of the mitral valve; embolism of the anterior tibial artery; death; no necropsy.*

X., aged twenty-one years, a commercial traveler, was seen with Dr. Slemons, of Salisbury, Maryland, on March 18, 1899.

His *family history* was good. He had always been a healthy boy; had never had rheumatism or serious illnesses of any nature.

Present Illness. In the latter part of December the patient contracted gonorrhœa. Early in January, he began to have chills at irregular intervals followed by fever and sweating. After the first several chills the discharge disappeared. He kept about at work despite the fact that he felt ill. In February the right knee and ankle became somewhat swollen and painful and he had to give up work for several days. In a severe storm early in February he was subjected to great exposure, and on the 20th the chills and fever, which had continued, had so far exhausted him that he was obliged to give up work and go home. Since this time he had been in bed suffering from fever which, at times, had been more or less continuous, at other times intermittent and associated with excessively severe rigors. The duration of fever, during these paroxysms was often surprisingly short, the patient having sometimes as many as three attacks in twenty-four hours, the temperature falling with great rapidity in association with profuse, drenching sweats. He had become feeble and anæmic. The febrile paroxysms were often accompanied by vomiting. Several days before my visit, during a paroxysm, the patient suddenly felt a numb, tingling sensation in the right leg. Since then the leg below the knee had felt as if it were asleep; it was cold and he had been unable to move it as freely as the other, while the foot and calf had been somewhat tender.

At the time of examination the patient was in bed, on his back; well formed man; somewhat emaciated. The face was pale and sallow; the lips and mucous membranes, pale. There was marked pulsation of the vessels of the neck. The pupils were widely dilated; the respirations rapid and rather shallow. The patient looked very ill and was so weak that he was unable to tell a connected story of his illness, the effort to speak being very considerable. The tongue showed a black coat (peptomangan). The pulse was regular, of low tension, 33 to the quarter. The *lungs* were clear throughout.

Heart. Well marked pulsation in the fifth space just inside the nipple. On palpation there was a marked systolic thrill in the pulsating area. Dulness began at the second space above and did not reach the right parasternal line. No marked evidence of right-sided enlargement. On auscultation there was a very loud, blowing, systolic murmur which almost replaced the first sound at the apex and was heard throughout the axilla and back. The murmur diminished markedly as one passed inward and upward, but a soft systolic murmur, probably the mitral murmur transmitted, was heard all over the cardiac area. The second pulmonic sound was accentuated; the second aortic feeble but clear. In the tricuspid area the first sound was well heard in association with the murmur. The *spleen* was not palpable, though the area of dulness was markedly increased. *Liver* not remarkable. No ascites. In a rather poor light no petechiæ were visible.

The *right leg* below the knee was pale and distinctly cold as compared with the left. The posterior tibial artery was not palpable on either side. The pulsation of the anterior tibial was felt on the left but not on the right.

Urine (only one ounce obtained), high color; trace of albumin; sediment, on centrifugalization: Decolorized red blood corpuscles; leucocytes in considerable number; hyaline and finely granular casts with red blood cells and fatty degenerated epithelial cells adherent. Occasional free, fatty degenerated epithelial cells.

Blood. Fresh specimen. The corpuscles are pale; difference in size, more than normal; slight poikilocytosis; great increase in the number of leucocytes.

A differential count of a thousand leucocytes stained by Ehrlich's triple stain, showed small mononuclear leucocytes, 4 per cent.; large mononuclear and transitional forms, 5.6 per cent.; polymorphonuclear (neutrophiles and two or three mast cells), 90.1 per cent.; eosinophiles, 0.3 per cent.

No nucleated red blood corpuscles were seen. No cultures from the blood could be taken. The patient steadily lost ground and died within a week after the visit. There was no necropsy.

In this instance the direct association between the acute gonorrhœa and the development of the ulcerative endocarditis would make it in every way probable that the case was one of true gonorrhœal septicæmia.

CASE V.—*Male, aged thirty-five years; gonorrhœa; ulcerative endocarditis of the mitral valve; death; an unidentified bacillus obtained in cultures from the valves.*

X., male, aged thirty-two years, a lawyer, was seen in consultation with Dr. H. B. Deale, of Washington, on 2d June, 1899.

The patient had had the usual diseases of childhood. Four years ago, severe attack of typhoid fever lasting five weeks. Has been under treatment for several years for some throat affection.

On 1st April, after a hard winter, he began to feel very tired and thinks that he had an irregular fever coming on particularly in the afternoon, and lasting from three to five hours, followed by profuse sweating. The fever was occasionally preceded by a slight chill lasting from fifteen to forty-five minutes. There have been frequent headaches; loss of appetite; moderate diarrhœa. On further inquiry it was found that the patient had had gonorrhœa at about the time of the onset of his symptoms.

The patient was first seen by Dr. Deale on 13th May, 1899. The temperature was 103°, pulse 88. There was nothing abnormal about the heart sounds or quality of the pulse. The blood showed no malarial parasites. The fever ranged from 99° to 103°, the pulse from 76 to 104 during the first week.

On 18th May a loud systolic murmur was heard at the apex, transmitted to the axilla. About 27th May the temperature became higher and the pulse much more rapid with periods of marked irregularity. Widal tests on 20th and 24th May were negative.

2d *June.* The patient was an emaciated, anæmic looking man, somewhat cyanotic; respirations rapid and rather shallow; vessels of the neck pulsating markedly. Pulse 34 to the quarter, partly from excitement, of rather low tension. *Heart.* The apex impulse was palpable about in the mammillary line. There was a loud systolic murmur which almost replaced the first sound, and was heard well through the axilla and back. The murmur was barely audible at the base; the second pulmonic sound sharply accentuated. At the tricuspid area and over the greater part of the right ventricle the second sound was somewhat reduplicated, having a sticky character; slight suggestion of a diastolic murmur. The second aortic was feeble but clear. The *lungs* were clear on percussion. On auscultation, fine, sticky râles were heard at both apices and bases, and, to a certain extent, along the anterior borders of the lungs, while the respiration over the middle of the right back was rather feeble. The *spleen* was not palpable, although the area of dulness appeared to be increased. The diagnosis was ulcerative endocarditis of the mitral valve probably gonorrhœal.

The patient died on 3d June.

The necropsy by Dr. Carroll showed that the heart was much enlarged; the left ventricle markedly hypertrophied. The walls of both ventricles were thickened. The aortic valves were competent with the water test and quite normal. "Both flaps of the mitral valve support large, irregularly shaped, pendulous masses of new formation which project from one-fourth inch at the margin, to about three-fourths inch at the centre, into the cavity of the ventricle. The leaflets of the tricuspid valve showed a slight nodular thickening along their margins. Cultures from the heart's blood, vegetations and from the liver on plain agar, human serum agar, Loeffler's blood serum mixture, blood agar mixture and bouillon revealed small, slowly developing, circumscribed colonies of small, slender bacilli often in pairs. These failed to grow on any transplantations. They were decolorized when treated by Gram's method. One of the Loeffler tubes from the heart's blood and one blood agar mixture showed these organisms in pure culture. The same organism was found in cultures from the vegetations in connection with a staphylococcus."

The close association of the onset of symptoms in this case with an attack of gonorrhœa justifies the suspicion that the urethritis may have served as the portal of entry to the infection, although evidence of its primary gonorrhœal nature is wanting.

Case VI.—*Man, aged thirty-one years; gonorrhœa; prostatitis; arthritis; ulcerative endocarditis (mitral insufficiency); death; no necropsy.*

H. G., male, aged thirty-one years; clerk. Family history good. Had always been a strong, robust man, rather given to athletics. Had never had any serious illness or previous venereal disease. Consulted Dr. S. Likes on 7th July, 1902, with a gonorrhœa of eight weeks' duration, which had been

treated by internal and local medication. Examination showed no discharge from the meatus. The urine was very cloudy by the test of the three glasses. The prostate was uniformly enlarged and the secretion following massage was very purulent and contained gonococci. The patient was put under treatment—daily massage of the gland, followed by mild permanganate irrigations. He began to improve until the prostatic secretion was almost normal and the urine clear.

On 24th July he had a chill followed by pain and swelling in both knee-joints. The chills recurred at irregular intervals, though the rheumatic symptoms soon began to abate, disappearing completely within a week. No local lesion could be found to account for the symptoms.

On 12th August I saw the patient in consultation with Dr. Likes. He was a healthy looking man, though the complexion was a little dull and sallow. The lung and heart sounds were clear. The spleen was palpable. The urine was free from albumin.

The chills and irregular fever continued and the patient was seen again two days later. At that time a soft systolic murmur was audible all over the cardiac area, rather harsher, perhaps, in the aortic area. The two sounds were of normal relative intensity.

Ten days later the patient was seen again. Irregular fever and chills had continued, although the patient felt quite well between attacks. The patient began to look somewhat anæmic and was clearly losing weight. The pulse was large and soft. The systolic murmur was audible, loudest at the apex, clearly heard as far outward as the anterior axillary line. The second pulmonic was accentuated; the apex impulse was 11.5 cm. from the median line. A specimen of *urine* was of normal color, acid, 1015, showing a slight trace of albumin.

From this time on the patient steadily lost ground. I saw him again on 10th October, at which time he had become more emaciated and anæmic. A systolic murmur similar to that before described was still audible. From this time the patient's condition grew gradually worse, chills recurring once or twice in twenty-four hours, although at one time there was a period of four days of normal temperature. From time to time Dr. Likes states there were attacks of violent coughing lasting about twenty-five minutes—about six of these attacks in all. There was marked and progressive anæmia with enlargement of the spleen and local tenderness. At no time was there any pain over the cardiac area. The patient gradually lost ground and died on November 9th, one hundred days after the onset of the condition. Dr. Likes states that the cardiac murmur became louder in the latter days of the illness. No necropsy was allowed.

In this instance no cultures were taken from the blood, but the onset and course of the case were strongly suggestive of a true gonorrhœal endocarditis.

CASE VII.—*Man, aged twenty-one years; urethritis; epididymitis; intermittent fever; ulcerative aortic and pulmonic (?) endocarditis; arthritis; cerebral embolism; streptococcus pyogenes obtained from the peripheral circulation; death; no necropsy.*

Y., aged twenty-one years, seen in consultation with Dr. Y. on 27th October, 1903. Family history unimportant. Has been a healthy boy. Has never had rheumatism. In January the patient had an attack of urethritis followed later by an epididymitis from which, in the course of several months, he apparently entirely recovered. He has not, however, been well since this time. During the summer, especially in the latter part, he has had slight recurrent febrile attacks.

On 6th September he came home from Chicago and was put to bed by his father, who is a physician. The temperature ranged from 97° to 99° in the morning to 102° to 103° at night. There was considerable sweating. The heart was enlarged and tumultuous in its action; pulse, 90 to 110; respiration, 25 to 30. The appetite was good. He complained at times of soreness in the knees and muscles of the legs.

The patient, seen in the evening, was in bed; skin hot and moist; large frame, rather sparely nourished; somewhat pale and of a slightly yellowish complexion. Pulse, large and collapsing, suggestive of aortic insufficiency.

Heart. Well-marked heaving in the precordial area. The apex was in the fifth space about 13.5 cm. from the median line, outside the mammillary line. Dulness to the right, not especially increased. The impulse was heaving. On auscultation the first sound was dull and indistinct; the second, replaced by a slight diastolic murmur which became more marked along the left border of the sternum and was heard most clearly in the third and fourth left spaces close to the sternum; it was also heard in the aortic area. The first sound in the aortic and pulmonic areas was indistinct. Passing out over the lungs on either side a well-marked systolic murmur became audible, which was not distinctly heard anywhere in the precordial area. This was heard everywhere in the chest, front and back, in the erect and recumbent postures. The lungs were clear throughout. The spleen was just palpable. One or two petechial spots were to be made out on the chest and arms.

Urine. Amber color; acid; specific gravity, 1025; no sugar; albumin possibly a slight trace; sediment, very slight cloud; microscopically, a few hyaline casts; a few pus and epithelial cells. Centrifugalized specimen, stained for diplococci; none found.

A *blood* culture was taken from the right arm, about 6 to 7 c.c. of blood being drawn from the median basilic vein and immediately plated with melted agar. From this plate numerous large and small colonies grew, which were found to contain a large spore-bearing bacillus, doubtless a contamination. At the time of this examination I made the following additional note: "The remarkable feature of this case is the systolic murmur heard over the

lungs. The only instance in which I have observed a somewhat similar occurrence was that of Mr. B. at the hospital, who had a systolic murmur well heard over the left lung and not in the precordial area, which was supposed to be due to an aneurysm. At autopsy it was found that it was dependent upon a stenosis of the main branch of the pulmonary artery at the root of the lung owing to an extensive gumma. May the murmur in this case be due to vegetations situated in the pulmonary artery above the valves?"

A diagnosis was made of ulcerative endocarditis of the aortic valves, possibly of the pulmonic as well.

On 1st November, a letter was received from his father stating that on the morning of 24th November, "The patient, without any warning, was suddenly seized by aphasia." This, as a paraphasia, continues without improvement. Coincident with it he has at times some pain over the region of the third frontal convolution. Muscular soreness has been at times very prominent, no delirium or mental aberration. At times some mental depression and drowsiness. A large number of petechiæ have appeared over the body very small in size.

On 2d November, Dr. Howard saw the patient who was pale; cachectic; emaciated; mind clear; marked sensory aphasia; no evidence of pain in any of the muscles. The right knee on the inner aspect is slightly red, hot, tender and puffy as also are the right first and second metacarpo-phalangeal joints.

Heart. Point of maximum impulse in the sixth space outside the mammillary line. Impulse strong and heaving; no thrill. Relative cardiac dulness, increased to the left; almost 4 cm. outside the mammillary line. At this point there is a loud blowing systolic murmur transmitted to the axilla and over the body of the heart. The second is faintly audible. At the base there is a soft diastolic murmur, of maximum intensity in the second right interspace. No accentuation of the second. Pulse, regular, definitely collapsing. *Cultures* from the blood, taken in the same method as before, revealed a pure culture of *streptococcus pyogenes*.

The patient steadily lost ground and died within the course of a week.

In this instance again the relation of the ulcerative endocarditis to the gonorrhœa, while suspected, cannot be said to be positively proven. The history of its development following the complications of a severe urethritis is, however, a noteworthy circumstance, justifying the suspicion that, whether or not the process were primarily gonorrhœal, the urethritis may have been the portal of entry for the infection.

DISCUSSION.

Dr. Osler: In addition to the cases of mild gonorrhœal septicæmia such as Dr. Thayer has spoken of, and which are very difficult to recognize from typhoid fever, look at the temperature chart—I think it is only the demonstration of the organisms in the blood positively that would enable us to make the diagnosis. In addition to that group I think there is an acute pulmonary septicæmia which is sometimes mistaken for typhoid fever in the suddenness of onset and overwhelming toxic effect. I reported one such instance in which Dr. Howard regarded it as a case of typhoid fever in the beginning. The young man died within a week. He had gonorrhœa. There was intense septicæmia, endocarditis and a slight pocket of pus in one lobe.

Dr. Trudeau: I should like to ask if there were any joint symptoms in Dr. Thayer's case?

Dr. Thayer: There were no evidences whatever of any local complications; nothing except a urethritis.

THE CHLORID EXCHANGES IN NEPHRITIS, WITH SPECIAL REFERENCE TO THE DECHLORIDATION TREATMENT.

By A. O. J. KELLY, M.D., and CHARLES A. FIFE, M.D.,
of Philadelphia.

Note by Dr. Kelly.—It is with extreme regret that I am compelled to confess, as this volume of the Transactions goes to press, that the paper by Dr. Fife and me, already long delayed, is not completed. A short time after I presented the more or less incomplete results of our investigations at the meeting of the Association in Washington, one of our patients was readmitted to the University Hospital, and it seemed desirable to make a further study of his condition, especially his chlorid exchanges. It is this study that Dr. Fife has not yet been enabled to complete. We have, therefore, deemed it advisable to withhold the paper until the study shall have been brought to a close.

Our investigations comprise the study of five patients in the medical wards of the University Hospital, service of Dr. Musser and of Dr. Stengel, to whose courtesy we are indebted for the opportunity to study them. Three of the patients were the subjects of parenchymatous nephritis with marked edema, one the subject of acute nephritis following so-called rheumatic purpura, and one the subject of myocardial and valvular disease with anasarca. During the entire periods of observation the diet of the patients was under careful scrutiny; it was weighed and measured, and varied in character from time to time. While the patients were on what we term a "special" diet, the bread was made without salt, and the meat and potatoes were cooked and eaten without salt. Aside from this, the exact chlorid content of the food thus

prepared was determined by chemical analysis. From time to time definite measured amounts of NaCl were added to the NaCl ordinarily present in the food. Furthermore, the patients were weighed—usually daily.

The examinations of the urine comprised the determination of the daily amounts, the reaction, the specific gravity, the amount of albumin, the percentage and the total amount of chlorid (estimated as sodium chlorid), and the total nitrogen. The NaCl content of the feces was also determined—sometimes daily, sometimes for periods of days.

It is impossible to formulate trustworthy conclusions from incomplete studies, and it is only with the hope of lending continuity to the discussion that I venture at this time to repeat the tentative conclusions which I announced at Washington, and which are based partly upon the incomplete results of our own observations, and partly upon a study of the work of others: In health the chlorid output seems almost to parallel the chlorid intake, only a small amount of NaCl being discharged with the feces, sweat and expired air; and healthy subjects appear to be able, with comparative ease, and within a day or two, to get into NaCl balance, even with rapid changes in the daily amount of NaCl intake. During such periods of variation in the NaCl intake, the noteworthy changes in the urine consist of an inconstant and variable diuresis, variations in the total NaCl output, and a corresponding variation in the percentage NaCl content. In many cases of nephritis the conditions are not totally different from those of the healthy subject, but changes in the NaCl intake are not followed so promptly by corresponding changes in the NaCl output in the urine, and NaCl balance is more difficult to attain and to maintain than in the healthy subject. In any case of nephritis NaCl retention may occur in consequence of insufficient elimination. The retained NaCl appears at first to be deposited in the tissues, whence the percentage NaCl content of the tissues increase considerably (of which several investigators have furnished definite proof); in many cases there appears to be no retention of water at first, and the weight of the patient does not increase. Sooner or later, in addition to NaCl retention, water retention occurs,

and the patient increases in weight, without, however, exhibiting any manifest edema—the stage of pre-edema of the French. Finally, with increase in the retention of NaCl and of water, the final stage, that of manifest edema, develops. The NaCl retention appears to be the primary process, the water retention a secondary process; and while the NaCl retention is probably attributable to functional disturbances of the renal epithelium (deficient elimination), all of the factors concerned in the process are not yet understood. The NaCl excretion and the water excretion do not proceed hand in hand, and probably disturbances in the circulation are of considerable importance in the process. The percentage NaCl content of the urine controlled by the NaCl intake is of much value in estimating the severity of the renal epithelial lesions, more particularly with reference to edema. Increased percentage NaCl content following a period of low percentage NaCl excretion is a favorable prognostic sign; low percentage NaCl excretion, especially when it cannot be increased or increased only transitorily, and particularly when diuresis cannot be provoked, is a bad prognostic sign. The relationship of diuresis in nephritis to total NaCl excretion and percentage NaCl excretion needs further investigation. A "salt-free" diet (a diet containing a minimum amount of NaCl), without the use of other therapeutic measures, may result in the disappearance of even excessive edema, and the use of such diet seems to be a valuable and well-indicated measure in many nephritic subjects, and permits of considerable variation in the foodstuffs, provided their NaCl content be low. Finally, it behooves us to proceed with more caution than has been customary in the past in the use of saline solutions in nephritis; if indicated, we should use hypotonic solutions, or, in the bowel, distilled or sterilized water.

THE ELIMINATION OF CHLORIDS IN NEPHRITIS.

By JOSEPH L. MILLER, M.D.,
OF CHICAGO.

Widal and Javal recently called attention to the inability of many nephritics to eliminate sodium chlorid in a normal manner. The salt retained in the tissues required a certain amount of water to maintain it in the proper molecular concentration, thus leading to edema, and suggests this as the probable explanation of dropsy in nephritis. This chlorid retention was found chiefly in acute and chronic parenchymatous nephritis, and especially in patients who were edematous. The retention was not found in the interstitial form, and we know edema when it develops in these cases is usually of cardiac origin. They furthermore decided that the impermeability of the kidney to urea and salts did not necessarily go hand in hand, as in the terminal period of Bright's disease there may be marked retention of chlorids, but none of urea, phosphates or sulphates. They report a case of uremia with daily elimination of 28 grams of urea, but only 0.39 gram of sodium chlorid. For this reason they consider the chlorid elimination as a better index of the functioning power of the kidney than the excretion of urea, and that the unfavorable progress of a case is associated with reduced chlorid elimination. With the chlorid retention there is increased elimination of sulphates and phosphates, and as the chlorids increase these salts diminish.

Only small amounts of sodium chlorid are essential for the animal economy. According or Bunge a person upon a mixed diet requires daily 1 or 2 grams; most people, however, consume 10 to 20 grams. The excess of chlorid is eliminated chiefly through the kidneys. The normal feces contain less than a gram daily; however, as a result of diarrhea this may be increased to 4 or 5 grams. The skin eliminates on an average 1000 c.c. of sweat, containing 1 to 2 grams of sodium chlorid. The total

daily elimination may, of course, be greatly increased by sweating, and some recent results point to increased sodium chlorid in the perspiration of patients with chlorid retention. In diseases associated with polyuria, as diabetes insipidus, or interstitial nephritis, the sodium chlorid intake and excretion may be greatly increased, often reaching 25 to 30 grams daily.

The view is generally held that when a large excess of sodium chlorid is administered to a healthy person, this rapidly appears in the urine, the maximum excretion occurring three to four hours after ingestion. Since the work of Widal, further study has been made of the normal kidney, and it has been found that the daily elimination of sodium chlorid suffers wide daily variation without any apparent cause. Koziczkowsky found upon a fixed diet the daily elimination varied from 9.9 to 23.7 grams in one case and from 6.8 to 14.4 grams in another. He gave people with apparently healthy kidneys an additional 10 grams of sodium chlorid daily for three successive days, having previously estimated the daily output, and reports a chlorid retention of from 18 to 25 grams.

Patients with acute or chronic parenchymatous nephritis when given, in addition to their usual diet, 10 grams of salt, show only moderately increased chlorid in the urine. Except in very severe cases, the amount of urine is increased. When this increased ingestion of salt is continued for several days the patients gain in weight, due to the developing edema; the amount of albumin in the urine is increased; headache, nausea and stupor may develop; in short, a condition resembling uremia. Widal and Javal were able to make the edema appear and disappear at will by increasing or withdrawing the chlorids. The weight of one patient fluctuated from 56 to 60 kilos. The edema rapidly disappeared when the patient was placed either upon a milk diet or upon meat, bread and potatoes. The addition of 10 grams of salt to either diet interfered with improvement. During the disappearance of the edema the daily amount of chlorids eliminated exceeded the intake 3.3 grams. The amount of albumin also decreased from 15 to 3.38 grams daily. When 10 grams of salt were added to the milk daily the urine decreased in amount and the daily retention of chlorids was 4.57 grams, the patient increasing 2.1 kilos in weight, the albumin increasing from 2.4 to

12.12 grams. The patient was then placed upon a diet containing 400 grams of meat with bread and 2500 c.c. of fluids. Within eleven days the weight decreased 3.7 kilos and the albumin had fallen to 0.72 gram daily, the edema reappearing when the salt was added to the diet.

Numerous investigators have verified the above results. Koziczkowsky reports marked increase in the amount of chlorid in the various organs of patients with uremia. Courmont, in three cases of acute or subacute nephritis, injected subcutaneously normal salt solution. After the second day the urine became scant and two of the patients developed uremia. Nagelschmidt produced an artificial nephritis in dogs, and demonstrated chlorid retention with increase of salt in the blood. Castaigne demonstrated that in animals with nephritis moderate amounts of sodium chlorid would double or triple the amount of albumin. He also reports that in patients with nephritis without albuminuria, after the administration of salt, albumin appeared in the urine.

Kovesi has recently verified Widal's results and given some interesting additional information. Patients with chlorid retention increased in weight and became more edematous after ingestion of excessive amounts of salts, although the fluids taken during this time were not increased and the daily amount of urine not diminished. It must be that the elimination of water by other channels has been lessened. There was no increase in the liquids passed in the stool and there only remain the skin and lungs. He believes, as a result of chlorid retention, there is a lessening of the invisible perspiration. The amount of evaporation which takes place from the surface of the body is dependent not only upon the moisture and temperature of the surrounding air, but also upon the molecular concentration of the body fluids. The higher the osmotic pressure the less water is given up.

Soon after Widal's communication the writer began investigating the subject. The cases for study were obtained chiefly from the wards of Cook County and the Presbyterian Hospitals. While no attempt was made to determine the exact intake of salt, the patients were kept upon a fairly uniform diet during the period of investigation. In some cases this was milk only; in others, the light ward diet. The chlorids were estimated by the Volhard method. When possible the patients were weighed daily. The

sodium chlorid was administered at first in wafers, but as this often produced nausea it was later given in solution. The following method was pursued: The chlorids were estimated daily for nine consecutive days. The first three days the patient had merely the chlorids contained in his food. The following three days he received daily an additional 10 grams; then the three following days merely the chlorids in his food.

In the following table the total urine for each of the three days' periods is noted, the total chlorid in each period, the grams of chlorid retained at the end of the period when extra salt was given, and the percentage of it in the urine during each period. During the second period 10 grams of salt were administered daily, except in the cases indicated by an asterisk, where only 5 grams were given.

Case.	Urine, 3-day periods.	Chlorids, gms.	Retained chlorids, gms.	Gms. chlorids per liter.
1. Acute nephritis, moderate edema	1 1680 c.c. 2 2050 " 3 2190 "	13.58 18.14 15.41	25.44	8.0 8.9 7.01
2. Acute nephritis, marked edema	1 6950 " 2 6300 " 3 7500 "	31.8 36.14 19.5	10.66 [1]	4.5 5.7 1.6
3. Chronic parenchymatous nephritis, marked edema myocarditis	1 1150 " 2 970 " 3 2380 "	1.0 1.86 2.32	29.14	0.86 1.91 0.97
4. Chronic parenchymatous nephritis, marked edema	1 4050 " 2 4100 " 3 3360 "	20 0 35.07 18.52	14.93	9.9 8.5 5.6
5. Chronic parenchymatous nephritis, marked edema	1 5090 " 2 5300 " 3 7440 "	17.55 38.64 31.66	8.91	3.4 7.1 4.2
6. Chronic parenchymatous nephritis, slight edema	1 3500 " 2 3800 " 3 3725 "	30.0 40.0 29.25	20.0	8.5 10.5 7.8
7. Chronic parenchymatous nephritis, marked edema	1 4600 " 2 3800 " 3 2950 "	28.06 24.96 20.51	33.1	6.1 6.5 7.0
8. Chr. parenchymatous nephritis, prob. secondary contracted kidney, no edema	1 4050 " 2 5580 " 3 4270 "	33.30 55.0 21.75	6.7 [2]	8.2 9.8 5.1
9. Chronic parenchymatous nephritis, no edema	1 6950 " 2 6300 " 3 7500 "	31.8 36.14 19.5	10.60 [1]	4.6 5.7 2.6
10. Normal	1 5340 " 2 5970 " 3 5040 "	37.41 44.75 87.45	22.66	7.0 7.5 7.4
11. Normal	1 6870 " 2 9120 " 3 7090 "	48.8 67.4 56.4	11.4	7.1 7.3 7.9
12. Normal	1 7580 " 2 7780 " 3 5520 "	37.62 54.7 44.4	12.92	4.9 7.0 8.0
13. Normal	1 3000 " 2 4000 " 3 3300 "	42.84 49.20 36.76	23.6	14.28 12.3 11.1
14. Myocarditis general edema	1 3906 " 2 9840 " 3 2108 "	24.0 78.0 13.0	24.0 [2]	6.1 7.9 6.1

[1] Patients received five grams extra chlorid daily.

[2] Eliminate in excess of chlorids ingested.

Two cases of acute nephritis were examined, one postdiphtheretic with blood, epithelial and granular casts, but only a trace of albumin. There were marked uremic symptoms and moderate edema. The other was of six weeks' duration, the urine containing a large amount of albumin, many granular and epithelial casts, very slight edema. These patients were kept upon an exclusive milk diet consisting of 1000 c.c. of milk and 250 c.c. of cream. One patient had a chlorid retention of 10.7, the other 24.8 grams. In both there was a visible increase in the edema. One patient was weighed, gaining three pounds during the period when extra chlorid was given and losing it quickly after the salt was discontinued. In one case less urine was passed during the period of extra chlorid than in the preceding or following period. The percentage of chlorid in the urine was increased following the administration of the salt.

Seven patients with chronic parenchymatous nephritis were examined. Six had more or less edema. The patient without edema had probably a secondary contracted kidney. The six patients with edema all had a chlorid retention, varying from 8.9 to 29.24 grams during the three days of extra salt. The secondary contracted kidney eliminated 6.7 grams more chlorid than was ingested. In two cases the urine decreased in amount during the period of extra chlorid. Two patients showed marked increase in the edema, and both complained of increased headache and stupor. One patient was taking Basham's mixture. A later test was made with patient taking 2 grams of diuretin daily, with much better chlorid elimination. The patient with the least chlorid retention died; the one with the greatest retention left the hospital much improved. In two cases with marked edema the albumin was estimated by the Purdy method, and the effect observed of potassium acetate, potassium neutral phosphate and theocin upon the chlorids and albumin. The results were practically identical in the two cases. During the period of extra chlorid the albumin was decidedly increased. None of the remedies used increased the elimination of chlorid.

Two patients with uremia were examined. Both of these died before the tests were completed, so do not appear in the table. In both cases the urine was scant and the daily amount of chlorids less than 2 grams. Following the administration of salt the

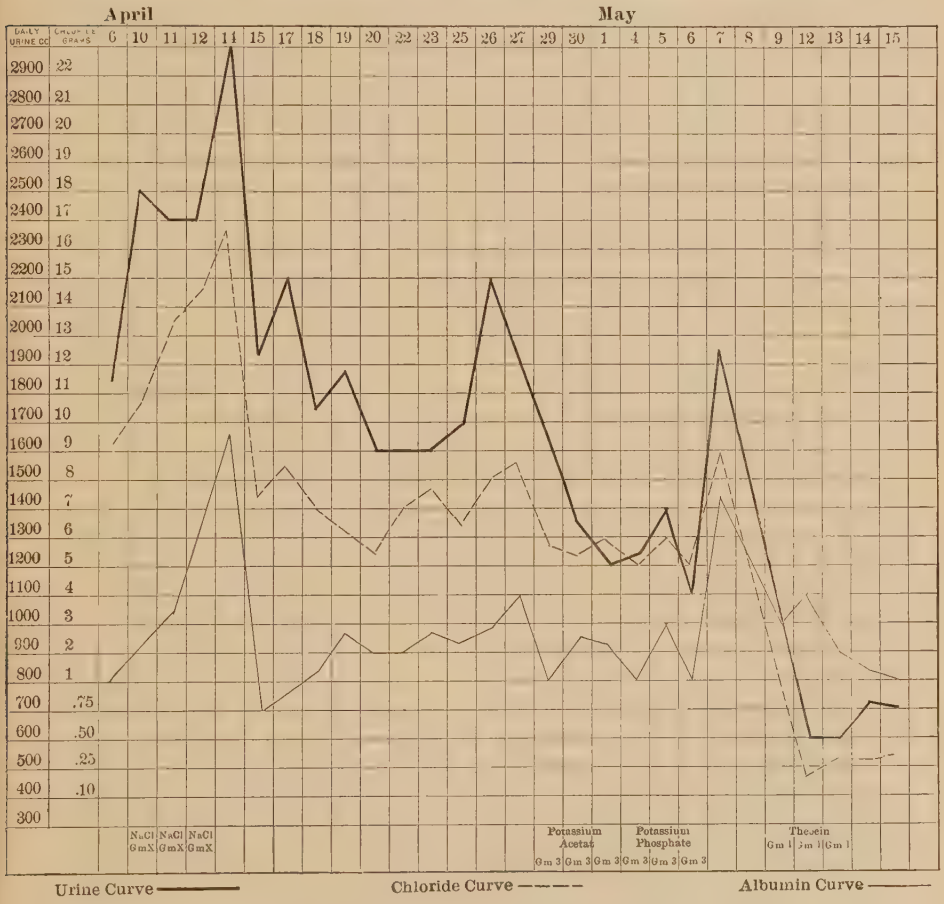
urine was lessened one case from 500 to 240 c.c., and scarcely any of the extra chlorid appeared. The edema was decidedly increased and the patient's condition worse.

A patient with myocarditis having fluid in the pleural, pericardial and abdominal cavities showed marked increase in the daily urine following the administration of chlorids, and excreted 24 grams, or 8 grams daily more chlorid than was ingested. This patient showed actual improvement, which continued after the chlorid was discontinued. This might be considered an increased activity of the kidney, due to the ingestion of large amounts of chlorid, analogous to the results of Claude, who found increased elimination of urea following the use of chlorids, or the results of Roque and Lemoine, who found increased activity of kidney to the phloridzin test after the use of common salt. In a single case of this sort, however, no conclusion should be drawn. While we are unable to disprove that excessive sodium chlorid stimulates kidney activity in some cases, it appears doubtful, especially when we consider its action upon the healthy kidney.

Four patients without apparent heart or kidney trouble were tested. All of these showed a degree of chlorid retention almost, if not quite, equal to the nephritics. This difference might be mentioned in two—viz., the retained chlorid was eliminated within forty-eight hours after its discontinuance, while in nephritics it took place more gradually. In each case the administration of chlorids caused a marked increase in amount of urine. Following the ingestion of the salt the percentage of chlorids in the urine was increased, not, however, to such a degree as in the nephritics. No edema resulted. Assuming that the salt was absorbed from the intestinal tract, it must have remained in the tissues associated with sufficient water to maintain the proper dilution; in other words, these patients had an undemonstrable edema. The tissues of the nephritics were already water-logged, so that any increase in edema was readily observed. In support of this view one of the patients was weighed daily and showed an increase in weight of two and a quarter pounds following the administration of the chlorids. Novecourt and Vitry's experiments upon nurslings is corroborative of this view. They administered daily for a period of seven days 0.25 to 1 gram of sodium chlorid, and found a greater increase in weight than for the same period upon the same

amount of food, but without the additional chlorid. They believe this is due to improved nutrition, but it is probably the result of water retention.

The daily amount of urine, sodium chlorid and albumin in a case of chronic parenchymatous nephritis are charted below. The



albumin curve was obtained by estimating the bulk of albumin in the centrifuge for the total amount daily. This percentage was multiplied by the daily urine in c.c. The curve, therefore, represents daily variations rather than absolute amounts of albumin. This patient was given various diuretics as indicated in the chart, without any perceptible effect upon the amount of urine or sodium

chlorid eliminated. It will be observed that the three curves follow each other very closely.

A summing up of the evidence would indicate that the chlorid retention in moderately severe nephritis is not greater than in the normal kidney. The terminal stages of nephritis, however, is characterized by very marked impermeability of the kidney to sodium chlorid. This difference, however, exists: in nephritics there is a visible increase in the edema; in the healthy individual there is no detectable edema. It is not necessarily true that a chlorid retention, after moderate excess of salt, exists in every healthy individual, but reports from various writers indicate that such is the rule.

Another phase of the question, and it would seem a much more important one, is the increase in the albuminuria and development of uremia symptoms following excessive chlorid ingestion. The view that the so-called uremia of nephritis is, in reality, a chloremia has little support. It appears that the increased cerebral edema is the more probable explanation. From a therapeutic standpoint, whatever the final decision regarding the impermeability of the nephritic kidney to chlorid, there is no doubt that excessive salt should be avoided, as it causes not only water retention, but by increasing the osmotic pressure of the blood lessens perspiration and the amount of water lost by respiration. Two grams of sodium chlorid daily are sufficient for the animal economy. Milk contains from 1.2 to 1.7 grams per litre. 100 grams of bread on an average 1.3 grams, 1000 grams of beef, 1.15 grams. Widal reports disappearance of edema and general improvement on a diet consisting of meat, 400 grams; potatoes, 1000 grams; sugar, 100 grams; butter (unsalted), 80 grams; fluids, 2500 c.c. This diet contains only 1.5 grams of chlorid. Especially to be avoided are the soups and broths, as they contain large amounts of salt, the broths at the Cook County Hospital containing 11.3 grams per liter, and many patients drink 500 c.c. of this daily. The use of subcutaneous injections of salt is contraindicated, as it may favor the development of uremia. The writer does not believe that the degree of chlorid retention is necessarily an index of the extent of kidney incompetency. Two cases of nephritis with a mild degree of retention died, while the patient with the highest degree of retention left the hospital improved.

CONCLUSIONS.

In patients with moderately severe nephritis associated with edema the ingestion of large amounts of sodium chlorid is followed by a chlorid retention. The patient gains in weight, the edema becomes more marked, the albuminuria increases, and symptoms may develop resembling uremia.

In patients with very severe nephritis, and especially those with uremia, chlorid retention is very marked, as scarcely any of the extra chlorids administered is eliminated.

In individuals with apparently healthy kidneys following the ingestion of sodium chlorid there is a chlorid retention equal to that of mild nephritis. The individual gains in weight, but there is no visible edema, no albuminuria, and no uremic symptoms.

REFERENCES.

Only a few references are appended. A complete bibliography may be found in Centralblatt für innere Medizin, 1905, No. 1.

Achard. Rétention des chlorures et pathogenie de l'œdème Soc. méd. des hôp. de Paris, 1903.

Achard. Hyperchloruration et dechloruration, ibid., 20 Nov.

Achard et Loeper. Rétention des chlorures dans les néphrites. Soc. méd. des hôp. de Paris. Maggio, 1902.

Castaigne et Rathery. La semaine médical, 1903.

Chaufford. Soc. méd. des hôp. de Paris, 1904.

Courmont. Lyon médical, 1903.

Illyes und Kovesi. Berlin klin. Woch., 1902, 1904, Nos. 24, 25, 26.

Nagelschmidt. Zeit. für klin. Med. Bd. xlii.

Strauss. Ibid., Bd. xlvii.

Widal et Javal. Presse médicale, 1903.

DISCUSSION.

Dr. Stengel: I wish to speak principally of the two patients that were referred to by Dr. Kelly as having been under my care, as I was able to watch them clinically throughout the period of this study, before as well as after. The first of these patients is the one which showed most remarkable improvement, a case of parenchymatous nephritis with some secondary arteriosclerotic changes. This patient was admitted to the hospital in a state of extensive edema and improved progressively during this treatment. The figures Dr. Kelly gives hardly convey to the mind the degree of improvement visible from time to time in that patient. There was great loss of weight, forty or fifty pounds, while he was under treatment, which can be accounted for by loss of water. The later increase in weight was due to improvement in his general condition. The entire aspect of this patient was changed. The

subsequent improvement in weight was quite evidently due to the improved general state of health, and not to reaccumulation of liquid. In the second case the patient was one who had been under my care previously and had a very bad form of nephritis. This patient came to the hospital while I was out of the city, and on my return I found that my house doctor had ordered enteroclysis, giving a quart of normal salt solution at a time, as the patient was apparently in a desperate state and the symptoms were getting rapidly worse. When I found this treatment ordered I asked him to discontinue this and substitute distilled water instead. From that time there was a very apparent improvement. I am sorry that Dr. Kelly was not working on that particular patient at that time, because if the amount of salt could have been estimated, given the amount of excretion and retention, it might have added materially to the interest of that case. I shall refer only to one other case, which is not supported by any chemical investigation, a patient who has since been in my service in the University Hospital, a private case, therefore not so available for study, a man aged thirty-six years, who had acute nephritis eight or ten years ago. Since then he has had repeated attacks of failing compensation of his kidneys, and has developed a high grade of arteriosclerosis and has the highest blood pressure I have ever seen in a human being. Estimates I made of his blood pressure after some of his periodical headaches read something like 280 mm. of mercury for the systolic pressure and over 200 mm. for the diastolic pressure. This patient told me, without suggestion on my part, that he was an inordinate salt eater. My treatment consisted in stopping this and regulating his diet otherwise, generally in the direction of reduction of salines, and I can say clinically the improvement in this case has been very remarkable, both in the matter of his headaches and also in regard to the blood pressure, which is a more certain indication, for that is systematically and continuously followed. The man is in a very good state.

I have been interested in this question of sodium chlorid since the publication of some of the earlier French articles, and I have felt hopeful that we might have in it a criterion for estimating the functional efficiency of the kidney. I am impressed with the inadequacy of other methods of determining what the kidney is really accomplishing, especially with regard to its sufficiency, and consequently the prognosis in a given case of renal disease. The quantitative determination of albumin has been, so far a I am concerned, completely discredited excepting in extreme cases. The method of determining the molecular contents of the urine or the freezing point seems void of any great value, and for clinical purposes is impracticable. If we have in this study of the chlorid excretion a means of determining the probably efficiency of the kidney it will be very helpful. From figures presented by Dr. Kelly and Dr. Billings for Dr. Miller, it would seem that the lack of accounting for excretion of sodium chlorid through the stomach and bowel constitutes a deficiency or shortcoming in many of the studies of the question. As Dr. Kelly has

pointed out, this may account for the differences in the results in his third patient, the patient in whom there were somewhat paradoxic conditions. This is paralleled by what clinicians have found in determining the quantity of albumin in the urine. Such determinations are notoriously of little value in estimating the probable severity of a case. After all we have to fall back on general considerations and a survey of the condition of the patient from various points of view. I am impressed from what I have seen of this work and of the practical application of the salt-free diet in nephritis that it constitutes a hopeful line of study. I feel that the matter is one of great importance, though not of as much importance as French writers would have us think. At least it is a slight step in advance in the treatment of these cases. To refer to another subject, while Dr. Barker was speaking, I recalled the communication to the British Medical Congress, made three years ago by von Noorden, on the analysis of different forms of meat and the availability of different forms of meat in nephritis. His views are, of course, well known that red meats are quite as admissible in chronic nephritis as white meats, and he proceeded altogether in the line of determining the extractives in meat, thinking that the only important difference from the point of view of the kidneys, found in meats of different kinds is in the extractives. This sodium chlorid work has shown us that some factors that have not been taken into account may, nevertheless, be those which will determine the usefulness of a certain form of diet.

The clinician has found to his satisfaction that for some reason milk is a very useful diet in the management of cases of nephritis. It may be the lack of sodium chloride.

Dr. Kinnicutt: A very practical point with reference to modern therapeutics is suggested by Dr. Miller's and Dr. Kelly's papers—viz., the possible evil effects of the introduction of large quantities of salt solution into the system, a therapeutic measure which, in the form of enteroclysis or hypodermoclysis, is at present so much in vogue.

During the past year, on the basis of investigations referred to by Dr. Kelly and of others, made in the laboratory of the Presbyterian Hospital, they have been used with much greater caution than formerly.

Dr. Edsall: Three years ago I made some fragmentary observations that have some relation to this question. I was particularly interested in the possibility of producing or increasing incompetency of the kidneys by administering large amounts of sodium chlorid; and this was of especial interest to me in relation to the use of hypodermoclysis in renal disease and in other diseases, in which the kidneys are perhaps already overtaxed, as, for example, in infectious toxemias. I was led to these observations by the work done by Steyrer while I was in Kraus' laboratory in Graz. The chief point in Steyrer's work in this relation was that after nephrectomy in a normal dog the remain-

ing kidney excreted very poorly for some time, and if a large dose of sodium chlorid were given at this time it seemed clearly to overtax the kidney and to lead to a poorer excretion than had occurred just before. After a little, however, the kidney became capable of carrying on the normal excretion perfectly well, and also of excreting added amounts of sodium chlorid. My observations consisted in the administration of 10 grams of sodium chlorid, divided into three doses, to persons with various forms of disorder of the kidneys. The result was to show that at times marked diuresis occurred and the excretion became larger than it was before, the amount of sodium chlorid excreted being sometimes even larger than the previous amount plus the quantity administered. In other cases, however, the total excretion of the kidneys, of water and solids, became greatly reduced, and even the quantity of sodium chlorid fell below that excreted before the extra dose was given. Steyrer thought that this method might have some value as a means of determining the functional capacity of the kidneys, but I believe that he relinquished this view himself, and my observations led me to conclude that it could not be very valuable as a diagnostic measure because the results were so irregular and did not seem to bear any constant relation to the severity of the kidney disease. I was convinced, however, that the free hypodermic or intravenous use of sodium chlorid solution in cases in which the kidneys are already severely taxed may have evil results. In some cases, as I noted, excretion was evidently increased, but in others it was reduced to what seemed a somewhat dangerous point. One patient, an arteriosclerotic, who had previously no evidence of marked renal incompetency, showed a reduction of the total amount of urine to below 500 c.c., the chlorids and other solids became greatly reduced, and the man actually became ill and had decided disturbance of his gastrointestinal tract for several days, with other appearances of toxemia. He gradually recovered and reached his previous condition. Since that time I have not often used hypodermoclysis in large amounts, and I prefer when using salt solution in this way or by the bowel to use a half-normal solution, and, indeed, frequently give distilled water instead through the bowel. I did not carry my observations sufficiently far to make it worth while to publish them, because I felt that the method was not a safe one to use further.

Dr. Meltzer: The fact that a certain amount of chlorids does not reappear in the urine should not be taken as a sure proof that it is retained within the body. They might have been discharged through the bile into the intestinal canal, or they might have been eliminated directly through the mucous membrane of the gastrointestinal canal. I believe that Dr. Kelly has mentioned that in many of the investigations the intestinal discharges were not examined for chlorids. I am afraid that many of the chlorid retention investigations are hardly capable of yielding any reliable results; they were begun at the

wrong end. The question is a physiologic and pathologic one, which can hardly be decided by observations on the therapeutic effects of withholding chlorids. The belief in a therapeutic measure rests a good deal upon the temperament of the observer.

Perhaps I may be permitted to make some remarks now which should have been made yesterday in the discussion on Dr. Sawyer's paper. It is on the value of sodium chlorid as a factor controlling the osmotic pressure of the fluids of the body. Dr. Sawyer told us his interesting experience that by washing out the stomach of patients suffering from diabetes he invariably relieved them of their thirst and polyuria without reducing the elimination of sugar. Perhaps the following suggestion will explain this observation. Sodium chlorid controls the osmotic pressure of the body; it attracts a certain amount of fluid from the body tissues into the lymph. In diabetes the tissue fluid of the body contains sugar, which also exerts a strong osmotic pressure upon the cells and attracts water. This is probably the cause of the thirst and partly also the cause of the polyuria. In washing out the stomach the body is deprived of hydrochloric acid, and with it some of the chlorids. This reduction in the possession of chlorids reduces the osmotic pressure; that is, it reduces the attraction of water from the tissues, and as a consequence thirst and polyuria are diminished, while the amount of sugar remains unaltered.

This view might have a practical application. If Dr. Sawyer's observation is confirmed and my interpretation of it is correct we could attain the same end by withholding chlorids from a diabetic patient.

Dr. Kober: In this connection it may be well to recall the fact that Bennett, Beal and others over fifty years ago called attention to the retention of the chlorids during the exudative stage of pneumonia and their reappearance in the urine during resolution. During my student days I attributed this phenomenon to diminished introduction of the chlorids with the food, and that the small amounts which represent the ingo and tissue waste may be eliminated in the secretions of the skin and mucous membranes. (Kober's *Urinology*, pp. 59, 60.) I know, however, very little of this subject, and it would be interesting to learn whether a satisfactory explanation has ever been offered.

Dr. Cabot: I should like to ask Dr. Kelly whether we have at present any knowledge which would make us discountenance excessive eating of salt in perfectly well persons. It is said that those who have kidney trouble ought to be discouraged from heaping salt upon their food or taking salt in quantities. Is there any reason why we should say to well persons, "That is a risky thing to do?"

Dr. Sternberg: We had some years since a medical officer in the army who was thoroughly convinced that various ills from which he suffered were cured by eating salt-free food. He believed that salt was really a poison and

he advised all his patients and everyone he met to leave off the use of salt. He wrote a paper on the subject, which is to be found on file in the Surgeon-General's office. There are no scientific observations in it except observations on his own case. He certainly carried it to a great extreme.

Dr. Jacobi: I should like to ask what is the experience of the members of this Association thus far of salt-free food in epilepsy. Certainly the question comes in here appropriately. There must be some experience accumulated on that subject.

Dr. Collins: I have had some experience in the treatment of epilepsy and also of the edema accompanying chronic Bright's disease by salt starvation or dechloridation. An experience that entitles me to the expression of an opinion concerning its utility. Two years ago I took twenty-four cases of epilepsy that were under daily observation and had been through various methods of cure, particularly the Flechsig method of opium bromid and the formal treatment of epilepsy. As a result of putting them on a diet free from salt these twenty-four cases have shown during the two years a reduction of 38 per cent. in frequency and severity of their epileptic attacks. More than that the attacks can be controlled by smaller doses of bromid, more than was needed when they were taking the ordinary diet. I have recently taken five cases of epilepsy which have been under observation in the dispensary, and therefore the opportunity was not so good to watch them carefully or make investigations upon them. In four out of these five cases the attacks have been diminished in intensity and frequently upward of 50 per cent. There seems to be no doubt from my own experience and from the experience of others who have had this matter under consideration since the idea was first suggested by Toulouse and Richet that a salt-free diet is a most important element in the treatment of epilepsy, and whether or not it brings about a reduction in the number and severity of the fits by its effect upon the constructive metabolism or by substitution of the salts of chlorin by the bromid preparations we are, of course, unable to say.

In answer to Dr. Cabot's question, I think it may be said that a normal individual can take as much salt as he wants, so long as his kidneys and blood-vessels are normal, just as he can almost anything else that amuses, amazes or contributes to his pleasure under the same desirable circumstances.

Dr. Tyson: I wonder how many of those present remember the studies of the effect of salt upon the diet of lower animals, published in that one time most popular text-book, Walton's *Physiology*. There we are told how the removal of salt from the diet of cattle resulted in the deterioration of their health, a change in the texture of their hides and the smoothness of their coats. It is interesting in this connection to reveal these facts.

Dr. Kelly: I can make merely a passing reference to some of the remarks in the discussion and the questions asked. In reply to Dr. Cabot's query, I have no personal knowledge whatever of the effect in a healthy subject of the ingestion of large quantities of salt. My knowledge comes altogether from the literature, and the consensus of opinion seems to be that under such circumstances the output almost parallels the intake, though a chlorid balance may not be established immediately. Some experiments go to show, however, that the prolonged ingestion of large amounts of NaCl is followed by deleterious effects on the kidneys. I am afraid that Dr. Meltzer did not altogether understand me: the chlorids in the feces were carefully investigated in our patients. To overlook this avenue of excretion would be a very serious error. Judging from the large amount of chlorids in the feces of one of our patients who had fluid, diarrheic stools, and who was excreting very little chlorid in the urine, I am confirmed in the opinion (of which, of course, there is much additional evidence) that the diarrhea of the nephritic patients is one manifestation of nature's attempt to rid the system of deleterious substances. The fact that the diarrhea of nephritis should not be unceremoniously stopped has long been recognized; in the increased chlorid excretion by the bowel we have one reason why the diarrhea should not be stopped. Dr. Tyson's remarks apropos of the effect of the withdrawal of salt from the diet of cattle recalls to mind an observation of Widal and Javal, who, pointing out that dairymen are in the habit of adding salt to the diet of cows, suggest that the withdrawal of such salt might give a milk better adapted than ordinary milk to nephritic patients; that is, a milk containing even less chlorid than is usual. I have no personal knowledge whatever of the effect of the withdrawal of salt in epileptic patients.

Although this has been an interesting study, many subjects still await solution, of which I might mention the relationship between diuresis and chlorid excretion; the relation between the chlorid excretion and that of other salts, especially the phosphates; the relationship between chlorid excretion and the excretion of substances, like methylene blue, etc., which some observers have found to bear no relationship whatever the one to the other, etc.

THE RELATION OF STOMACH DISORDERS TO DIABETES MELLITUS.

By JOHN P. SAWYER, M.D.,
OF CLEVELAND, OHIO.

The several published studies which I have found upon the stomach in diabetes have been concerned with the attempt to trace a definite relation between the secretion of the stomach and the excretion of sugar. All have reached the same conclusion, that the variations in the chemical composition of the gastric juice occur without any parallelism observable in the chemical composition of the urine.

With this I fully agree, but in the work hitherto done the failure to find any mathematical parallelism in the secretions has caused the inference that because of this want of parallelism there could be no recognizable influence exerted from the stomach upon the process of diabetes.

The cases which I have to report will, I think, prove that the reverse is true, that from the stomach, or, at least, in association with digestion occurring within it, is exerted a powerful influence upon the clinical course of the diabetes, expressing itself in many cases in the heightening of the errors of metabolism which we recognize in the increased elimination of sugar and urea, with the clinical symptoms of thirst, hunger, polyuria, muscular weakness and emaciation.

It was the empirical idea of Rollo and his immediate successors that the stomach in some way was the cause of diabetes.

As physiologic knowledge grew it was seen that in any such way as had been supposed this was untenable.

With the introduction of the study of test meals came the researches of the '90s, showing the irregular chemical composition

of the gastric contents in diabetes. Apparently no attempt was published as having been made to treat the stomach in diabetes according to the measures which the study of later years has shown advantageous when that organ is the one primarily involved.

Because the analysis of the stomach contents cannot be found uniformly in this disease to be associated with uniform pathologic findings is not a sufficient ground for concluding that, therefore, the stomach may not be the starting point from which, or in which, errors of digestion begin; with the resulting error developed multiplied in the later process of metabolism, to the great detriment of the individual.

The following case histories show that some influence upon many of the cases was exerted by a direct attention to the condition of the stomach. The degree of this influence varies in varying cases, but of definite clinical importance the observations appear of value.

I will proceed directly to the report of cases, for the sake of brevity mentioning only pathologic findings or positive observations bearing upon the subject-matter.

Case I.—A young man, aged twenty years, from Ashtabula, O., consulted me April 13, 1903. He was discovered to be passing eight quarts of urine daily since last January after he had had an attack of ailment resembling the grip. (No better description could be obtained.) His best weight had been 117 pounds about January 1st, in February, 105 pounds, and on April 13th, 103 pounds. Previous to January 1st he had had a considerable amount of digestive trouble, frequent and severe distress being reported.

Physical examination showed a slender but, so far as the internal organs were concerned, an apparently healthy young man.

Examination of the urine showed a specific gravity of 1022, and the quantity of sugar amounted to 3.75 per cent.

A test-meal gave 80 c.c. of stomach contents which separated into three layers on standing, the top layer being one-third the column, free hydrochloric acid 40 c.c., total acidity 50 c.c.

The patient went to the hospital and was confined to the bed a greater portion of the day. A measured amount of exercise was allowed. Specimens of urine were saved, and lavage was begun for the catarrhal conditions of the stomach, using resorcin and followed by sodium bicarbonate. The treatment consisted of daily lavage and during his stay in the hospital he was kept upon the von Noorden standard diet for two weeks, no starch whatever being allowed. The quantity of urine of April 23d was 2700 c.c., and contained

2 per cent. of sugar. On April 24th the quantity of urine was 3600 c.c., 3.5 per cent. of sugar being present.

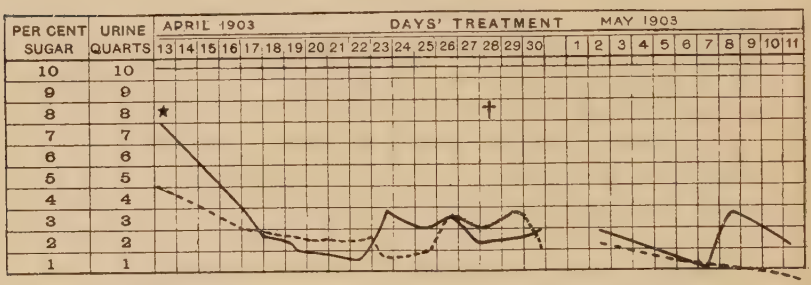
April 27th 2500 c.c. was obtained and the quantity of sugar was found to to be 3.75 per cent. by fermentation. Standard diet was now discontinued. On May 2d 2800 c.c. of urine was obtained and the quantity of sugar was found to be 2.5 per cent. by Fehling's solution.

On May 11th 1170 c.c. of urine was obtained and contained 1.55 per cent. of sugar.

On May 17th 0.6 per cent. of sugar was found by fermentation. The patient returned to his home and was under the care of Dr. Geib. Lavage was continued, and mashed potatoes and bread were allowed.

No sugar was found in his urine at this time, and frequent tests made throughout the following months showed no trace of sugar.

CASE I.


PER CENT SUGAR
URINE QUARTS
APRIL 1903
DAYS' TREATMENT
MAY 1903
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5 6 7 8 9 10 11
10 9 8 7 6 5 4 3 2 1
—— Quantity of urine.
---- Per cent. sugar.
* Lavage and standard diet.
† Standard diet stopped.

Treatment continued at home, urine became sugar free.

Twice small amounts reappeared for a few days only and now patient is apparently well.

During his stay in the hospital the catarrhal process persisted until just before his return home, and lavage was continued till the disappearance of the catarrhal symptoms rendered it unnecessary. Test-meals have not been taken by Dr. Geib, but the thirst of which the boy complained and his great hunger entirely disappeared while the patient was in the hospital.

The case is of peculiar interest from the fact that the persistent use of the standard diet for two weeks did not materially reduce the sugar, which, however, promptly disappeared upon the institution of lavage, and the allowance of bread and potatoes with fats—and in addition in recent months—a greatly increased quantity of finely ground starches.

The last of September a quantity of sugar was found in the urine, and he was sent back to me by Dr. Geib.

The twenty-four hours' specimen examined at the hospital showed 2.5 per cent. of sugar, and the quantity found was 1400 c.c.

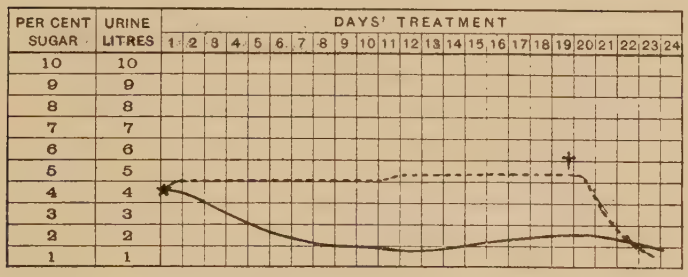
The examination of the stomach showed the recurrence of the catarrhal gastritis with a very heavy top layer of clumpy mucus and a considerable hyperchlorhydria. Thirst and bulimia had not developed. This case is extremely valuable in showing the reappearance of the glycosuria with the coincident reappearance of the catarrhal gastritis. After a few days' treatment by lavage twice daily the catarrhal gastritis and the glycosuria both disappeared entirely.

For the last year and a half the patient has continued the use of all kinds of foods, eating as usual from the family table, restricted only from the use of sugar and the taking of raw fruits. Twice only has he shown sugar in the urine, once for a few hours after the taking of a Christmas dinner, and once last summer after the indulgence in fruits and grapes.

At the present time he is reported as in apparent best of health and is at work as a clerk in a hardware store, weighs more than ever in his life, and for enjoyment taking a "stroll" of over twenty miles without any bad effects.

Case II.—C. S., a teamster, aged twenty-two years, had always had good health. His former weight was 170 pounds. He entered St. Vincent's Hospital November 16, 1903. During the spring he began to experience some slight dyspeptic distress, and then with continued loss of flesh thirst developed, the secretion of urine increased, and in May he was unable to work.

Case II.



—— Quantity of urine. * Lavage once daily.
---- Per cent. sugar. † " twice "

His urine was not examined till he visited the dispensary of the hospital, at which time a large quantity of sugar was found and he was sent into the hospital. His weight at that time was 128 pounds, a loss of 42 pounds.

The Ewald test-meal, taken one hour after ingestion, gave 50 c.c. of stomach contents, of which 40 c.c. was clumpy mucus with a strong reaction for hydrochloric acid. It was not determined quantitatively because the standard solutions were exhausted the day before.

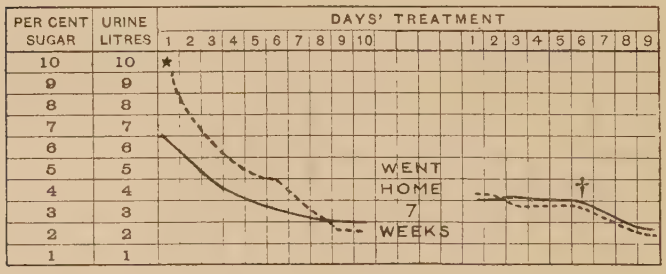
The quantity of urine was a little over four quarts, but it was not more accurately measured. Lavage was begun on November 17th, and continued

daily with sodium bicarbonate. The quantity of urine was 1900 c.c. with a specific gravity of 1040, by the copper reduction test 5 per cent. of sugar was found and by fermentation 5.2 per cent. These figures represent the daily determinations until December 4th, at which time the quantity was 2500 c.c. and 5.6 per cent. of sugar by the copper test was found, and by fermentation 5.6 per cent.

On December 4th I ordered lavage twice daily with a more alkaline solution, using a teaspoonful each of sodium bicarbonate and sodium biborate in a quart of water. The percentage of sugar promptly began to fall to 3, 2.8 and 2.4 per cent., until on December 8th the twenty-four hours' quantity of urine showed 1800 c.c. and contained 1.6 per cent. of sugar. The patient gained six pounds in two weeks. He felt so well that he decided to leave the hospital and went to work in some town in Michigan and I have no further knowledge of him.

Case III.—Mrs. H. consulted me at my office on Septemper 17, 1903. At that time the urine contained a quantity of sugar which was very large, about 10.5 per cent. by the copper test. This patient was twenty-three years of age and was well till two years ago, though she previously experienced weakness. She had lost much flesh, especially six months ago, when there was great loss in six weeks' time. She was passing seven quarts of urine a day. There is no history of diabetes in the family, she never had serious illness since her childhood, but for the past three or four years she has always felt a load in the stomach, with "bloating," as she expressed it, after eating.

Case III.



—— Quantity of urine. * Lavage once daily.
---- Per cent. sugar. † " twice "

The following day the twenty-four hours' specimen gave a percentage of 8.3 per cent. by copper and 8.3 per cent by fermentation.

The residue taken three and a half hours after ingestion gave 300 c.c. of stomach contents, showing great motor insufficiency, with 150 c.c. mucus top layer, 70 c.c. clear liquid, and 80 c.c. food substance. Hydrochloric acid was 16, total acidity 56. After the use of lavage for three days with alkaline solution and salicylic acid, separately used, the quantity of urine was

four and a half quarts, the copper reduction test gave 4.9 per cent. and fermentation 5.5 per cent. of sugar.

The specimen of urine on September 22d showed 5.0 per cent., on the next day 4.1 per cent., and on the following day 3.4 per cent., while the influence of lavage showed in a test-meal a considerable reduction of the residue 100 c.c. only being recovered, of which there was 5 c.c. clumpy mucus, 20 c.c. clear liquid, and 75 c.c. food sediment.

The patient meanwhile expressed the greatest relief from thirst and the excessive hunger, and on September 25th was passing three quarts of urine in twenty-four hours, showing 2.7 per cent. of sugar. She now felt so much better that she thought she would carry on the lavage at home. The conditions there were not favorable, and the percentage of sugar in the specimens rose to 6 per cent. and 7 per cent. until she entered the hospital about the middle of November, when 5.5 per cent. was found in the secretion of four quarts in twenty-four hours.

With lavage daily and quiet not much impression was made on this patient till December 4th, at which time the amount of sugar was 4.6 per cent. Lavage with stronger alkaline solution was ordered twice daily. The quantity secreted and the percentage diminished till December 8th, when the test for sugar showed 2.4 per cent by copper.

This patient gained five and a half pounds in three weeks and expressed the liveliest satisfaction in the increased strength and vigor. She returned to her home and during the month of January five urinary examinations were made, averaging four quarts a day, the specific gravity 1032, sugar 4.2 per cent.

Nothing more was heard from this patient till September 30, 1904, when a specimen was sent in, and found to be from three quarts in twenty-four hours, specific gravity 1032, sugar 4.6 per cent. At my urgent request she came for a test-meal October 5th and there was obtained 175 c.c. four hours after a Riegel meal, of which 150 c.c. was of a mucus and food residue top layer, with 25 c.c. of clear liquid at the bottom. Hydrochloric acid 20, total acidity 40. The specimen brought in this day reported to have been taken from a daily excretion of six quarts, specific gravity 1035, sugar 3.9 per cent.

She reported herself as doing her own housework, ironing but not washing. Says she is eating everything, but uses saccharine in her cooking. She has gained decidedly in her strength and in every respect is far better and far more comfortable than seemed possible to be the case a year age.

Case IV.—Harry J., of Alliance, O., a high-school pupil, aged fifteen years, consulted me August 11, 1904, with a history as follows:

As a child of eight or nine he had "yellow jaundice," none of the other infectious diseases of childhood till last April, when he had the so-called three-day measles—"rötheln."

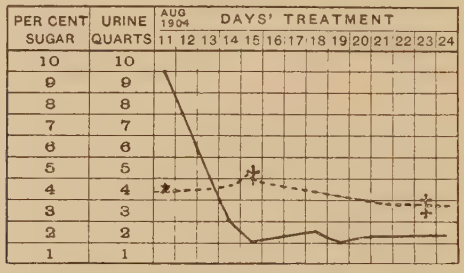
He began to have some stomach difficulty and shortly thereafter he developed thirst and polyuria. Sugar was found when the patient consulted Dr. C. M. Hoover and Dr. J. A. Roach, who referred him to me for consultation. August 12th the test-meal showed motor insufficiency, 80 c.c. of stomach con-

tents being obtained, the same separating into two layers, the top of clumpy mucus, about 50 c.c., the lower layer, 30 c.c., being clear liquid. Free hydrochloric acid 32 c.c., total acidity 46 c.c.

The urine for the twenty-four hours was ten quarts, specific gravity 1035, sugar 4.4 per cent. albumin absent, bile costive.

The patient was put upon the plan outlined, of alkaline lavage; the diet was by no means starch free, though excluding sugar and materials, which by their physical properties might irritate the mucous membrane.

CASE IV.



—— Quantity of urine. * Excreted 440 gms. glucose.
---- Per cent. sugar. † " 108 " "
‡ " 73 " "

Two days later the amount of the twenty-four hours' secretion was 2400 c.c., a little over two quarts; specific gravity 1032, sugar 3.4 per cent. From the first the patient's thirst was almost entirely relieved, the quantity of urine steadily diminished and his sense of well-being vastly improved.

He returned to his home to carry out for himself the practice of stomach washing and the use of the resorcin and chloroform-water before meals.

The patient has at various times returned to the hospital for a few days' observation and treatment, in the course of which various changes in the solutions used for washing the stomach have been made. Silver nitrate, hydrastis, salicylic acid, lysol, creolin, sodium bicarbonate and sodium biborate have been used. The patient has pursued his work in school, gained in weight twelve pounds, is not conscious of easy fatigue, feels quite well, does not suffer from thirst, but continues to excrete sugar in proportions from 2 per cent. to 4 per cent.

CASE V.—Ida R., a school-girl, less than fifteen years of age, consulted me April 4, 1904; was known to have diabetes for about a year, apparently following a typhoid or malarial attack. The glycosuria was recognized April 4, 1903, and she is known to have been quite thirsty for a short time before this. In the course of her disease she lost some flesh and had grown quite weak, her pulse being 120, but no elevation of temperature. In the family there is no evidence of other diabetics.

April 4th there were four and a half quarts of urine in the twenty-four hours, a trace of albumin, bile and indican absent, sugar 4.8 per cent. by copper test, urea 0.4 per cent. The test-meal gave 40 c.c. of stomach contents, no distinct separation, the whole mass being of a catarrhal character, hydrochloric acid 68, total acidity 104.

The patient was put upon alkaline lavage, with the resorcin and chloroform-water, and further with benzosol, 3 grains t. i. d.

April 8th, four quarts of urine in twenty-four hours, specific gravity 1028, sugar 3.9 per cent., urea 0.99 per cent.

April 9th, specific gravity 1028, sugar 3.7 per cent., five pints and six ounces secretion.

April 22d, five pints in twenty-four hours—"drunk but half a glass of water last night"—sugar 5 per cent. And so on through a great number of examinations which were made, the quantity ranging from five pints to three and a half quarts, percentage of sugar running on the average about 4.2 per cent.

The patient has gained in weight and strength and the quantity of sugar has not lessened in percentage, average secretion through June being five pints, percentage of sugar running from 2 per cent. to 3.9 per cent., once touching 5 per cent.

The patient has not remained under continuous observation, but has come to the hospital for short periods of time, during which the standard diet has been administered in several trials without producing the disappearance of the sugar.

In one of the late trials sugar disappeared for a single day after several days of standard dieting, but promptly reappeared.

Her condition at present is one of apparently good health, maintaining her weight and strength with a great degree of comfort, she is not troubled by thirst and feels so well that it is difficult to restrain her from overdoing.

The excretion of urine ranges from five pints to three quarts, and from 3.5 per cent. to 5 per cent. of sugar. During this period she has continued her strength and development, increasing apparently as a healthy person should do. But for a knowledge of the excretion of sugar she and her parents would think she was well.

Case VI.—Mr. G., aged twenty-three, married, one child, consulted me January 8, 1904. Two years ago he had first noticed at Thanksgiving time that he was passing a large quantity of urine at night. He had had no previous illness save pneumonia in childhood. The family history is one of good health. No tuberculosis, none of the family have had diabetes, one sister living, aged thirty-eight, is thought to have gallstones.

A twenty-four hours' collection of urine gathered and weighed by him at fifteen pounds—something over seven quarts—specific gravity 1027, albumin and bile both positive, indican absent, urea 0.35 per cent. By copper and fermentation 4.7 per cent. of sugar.

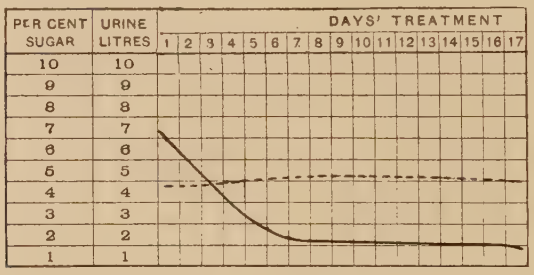
A test-meal taken January 9th showed 40 c.c. of stomach contents which

separated into two layers, the upper consisting of tough, clumpy mucus, markedly tinged with blood, indicating the severity of the process. Free hydrochloric acid 20 c.c., total acidity 60 c.c.

The patient was put at once upon the treatment outlined of alkaline lavage, the rest in bed with diet as in other cases.

The thirst and excessive urination diminished, and the test of January 15th showed 2400 c.c. January 23d the amount in twenty-four hours was 2130 c.c., specific gravity 1040. Copper and fermentation gave 5.4 per cent. and 5.3 per cent. respectively of sugar. January 25th the amount was 1800 c.c., 5.3 per cent. of sugar. February 16th, the stomach contents were markedly less catarrhal, but showed no free hydrochloric acid. February 17th the amount of urine was 2300 c.c., sugar 5 per cent.

Case VI.



—— Quantity of urine.
---- Per cent. sugar.

March 5th, 100 c.c. of stomach contents were obtained after a test-meal and showed practically no catarrhal process, hydrochloric acid 18 c.c., total acidity 26 c.c.

The patient reporting a very great gain in strength, has been feeling so well that he has gone to work on the farm, and in fact he worked hard in the sugar bush!

He reported during the summer that he continued to feel well, gaining in weight and strength. Sugar was still present, but polyuria, thirst and voracious appetite were absent, and without the assurance that sugar was still present he would have thought himself well.

This favorable condition continued until last fall, when I believe he went into other hands because of inability to come to the city for treatment, and was not doing well when last heard from.

Case VII.—Mr. R., aged twenty-six years, consulted me for a supposed Bright's disease. He has indulged somewhat in the use of liquor and six months ago weighed 223 pounds, now 165 pounds.

The residue of foodstuff in the stomach was catarrhal—abundant and exceedingly hyperchlorhydriac.

He has been very thirsty and passing large quantities of urine, which upon examination showed a specific gravity of 1032; neither albumin nor bile were present; urea 0.4 per cent., sugar 5.6 per cent.

This patient never had measured his urine, but said he "was passing gallons per day." He entered the hospital three days later, having had daily lavage, with great relief from thirst and excessive excretion.

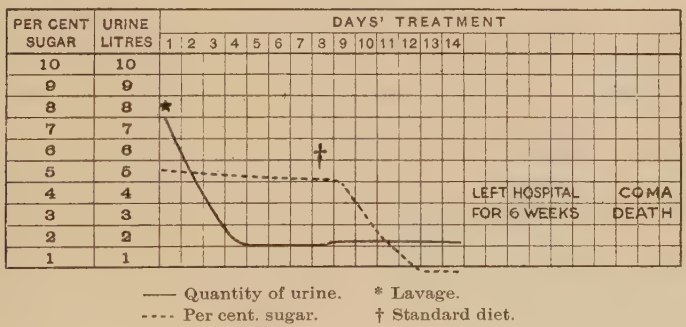
The 2d, 3d and 4th he passed an average of 2300 c.c. per day, 5.2 per cent. the average excretion of sugar.

Von Noorden's standard diet was now administered and the quantity of urine became on an average of about 2000 c.c., with an average of 0.8 per cent. At this time the craving for liquor asserted itself, and after a free indulgence he left the hospital with 2.2 per cent. in the twenty-four hours' secretion of 2060 c.c.

In December he was readmitted and died shortly after in diabetic coma.

Case VIII.—This patient is a physician and in active practice. I wrote to him a few days ago to secure a statement of his personal experience, on which I laid the more value as because of extensive laboratory and clinical training. I think him exceedingly well qualified to give valuable opinions concerning his experience.

Case VII.



—— Quantity of urine. * Lavage.
---- Per cent. sugar. † Standard diet.

"My glycosuria developed four and a half years ago and was ushered in by the cardinal symptoms of extreme thirst, polyuria, increased appetite, loss of weight and a sense of muscular and mental fatigue.

"Upon discovering sugar in my urine I went on a vacation and began a diet quite free from carbohydrates. The sugar all disappeared, but returned intermittently after a couple of weeks. I gained several pounds in weight and got stronger. I continued on the diet of meat, eggs, cabbage, etc., with a small allowance of gluten bread, for three years, taking very little carbohydrates at any time. My appetite was much exaggerated. I had frequent attacks of nausea and occasional vomiting, especially at night. I ate large quantities of food because I got no sense of satisfaction from the moderate amount, and even then it was an hour or so after a meal before I felt that I was getting any benefit of my food.

"After seeing you I have been relieved of the abnormal appetite. I now eat only an ordinary amount, have no thirst, am taking a small amount of starch at each meal, feel satisfied after eating, and have a sense of well-being."

He also writes: "Upon a proteid diet I had hunger, thirst, nausea, occasional vomiting, fatigue, and glycosuria. Under a bland, non-irritating diet, mixed proteid and carbohydrates, my abnormal hunger and thirst are gone. I can do far more work, without fatigue. I feel far better. When I get to feeling 'off' with either gastric distress or discover glycosuria I have gastric lavage with benefit."

Case IX.—June 30th, 1902, Mr. C., an attorney, aged fifty-four years, consulted me for a known diabetes which had been recognized a year and a half before. Previous to this he had a considerable dyspeptic trouble.

A twenty-four hours' secretion had never been obtained, but percentages of sugar ranging from 7.5 per cent. to 2 per cent. were reported to him from individual specimens.

He was troubled with thirst, polyuria, weakness, but not much loss of flesh.

A test-meal showed good motor sufficiency, 25 c.c. being obtained three and a half hours after ingestion, which separated into three layers; hydrochloric acid was 31, total acidity 54 c.c. Sugar 6.2 per cent. in the specimen submitted. The patient had been in the habit of rising three and four times per night and at times urinating every hour or oftener during the day.

Lavage was begun and there was prompt relief from the frequent urination, and the percentage fell in the twenty-four hours' specimen to 4.2 per cent. One week later, 3.6 per cent. Two weeks later, the quantity in twenty-four hours was one quart, three gills—1250 c.c., sugar 1.5 per cent.

At about these findings the case has continued for the past three years, rising occasionally to 3.5 per cent. or 5 per cent., but never with polyuria, thirst, and with sleep broken never more than once per night.

The patient expresses himself as much pleased with the marked gain in strength and comfort, which has come in spite of active participation in an active and responsible practice of law.

He has gained so much that he feels unwilling to limit, as I desire, the amount of work undertaken.

Standard diet and the "oat cure" have failed to entirely relieve the presence of sugar, although exercising a markedly favorable influence.

Case X.—Mr. M., a politician, aged fifty-six years, first seen by me October 29, 1904. For three years has known he had diabetes. This knowledge came after an attack of typhoid, during which he lost forty-five pounds, which were never recovered. Two years before this he had great thirst and hunger with as far as he knows increased polyuria.

The twenty-four hours' specimen measured six pints, 4.8 per cent of sugar, specific gravity 1040, urea 0.67 per cent., no albumin, bile positive. The scanty stomach contents obtained after a test-meal showed no reaction to hydrochloric acid.

This patient has continued to the present time passing five to six pints of

urine per day, percentage ranging from 4 per cent. to 6.5 per cent. The "oat cure" and standard diet have not reduced these figures, but under the diet and the use of remedies directed to the catarrhal condition, notably resorcin and chloroform-water, the patient has expressed himself as much stronger and with far greater endurance. This case has shown the least effect of all the cases treated with direct attention to the condition of the stomach, but is decidedly stronger than at the commencement, gaining six pounds in ten weeks.

Case XI.—Mr. R., seen in consultation with Dr. Merriam October 17, 1903.

This patient was a hotel clerk, aged sixty-four years, and when seen at his home confined to the bed, intensely icteric with a marked congestion of the liver reaching three fingers' breadth below the costal margin without enlargement upward. Dr. Merriam had found sugar in the urine three months previously, and continually thereafter.

The test breakfast taken showed good motor sufficiency, the gross appearance markedly catarrhal, quite blood-stained, no free hydrochloric acid, an abundance of lactic acid, and microscopically numbers of Oppler-Boas bacilli, and a very considerable amount of pus. The patient had been a free drinker for a number of years.

The examination of the urine showed 5.9 per cent. of sugar, no albumin, bile positive, indican absent.

He was advised to stop his whiskey, and a diet which was to be bland and non-irritating, but not starch free, was recommended, saccharine in the place of sugar being the only marked restriction upon his carbohydrates.

April 28, 1905, Dr. Merriam reports that on quitting alcohol, the use of lavage and rest at home he improved immediately, and at no time for more than a year past has any sugar been found in the urine either by copper tests or the polariscope, and the stomach disturbance has entirely subsided.

The glycosuria persisted too long to be an alimentary glycosuria simply, but the case may well have been an alcoholic diabetes, and of special interest is the severity of the catarrhal gastritis, which has disappeared also.

Case XII.—A diabetic referred to me by Dr. D. P. Allen. There was loss of flesh, considerable thirst, great hunger. There had been gangrene, necessitating the removal of three toes while the patient was under Dr. Allen's care at Lakeside Hospital.

When coming under my observation the percentage of sugar was 5.2 per cent. in the twenty-four hours' specimen. The patient was a large, fleshy man of over fifty years of age and of nervous temperament; no other essential findings were observed, save a catarrhal gastritis with hyperchlorhydria and motor insufficiency.

Lavage with creolin followed by sodium bicarbonate solution was begun, and, as he complained of his restricted diet, a considerable relaxation was allowed.

Under these measures the excretion of sugar rapidly diminished and soon entirely disappeared. The patient remained free from glycosuria for months,

at last going under the care of Dr. O. T. Maynard, of Elyria, who made repeated examination and found sugar only once in the course of a year, and then only after an unusual indulgence in a Christmas dinner.

Case XIII.—A gentleman aged fifty-seven years, large frame and good flesh, weighing 245 pounds, one year ago 250 pounds (a capitalist, actively concerned in the development of traction properties and banks, which entailed considerable nervous strain), consulted me on February 6, 1904, with a statement that he felt quite well till within the past two months. About six weeks before coming he had noticed that he was compelled to rise at night to urinate, and this had increased till he was up every hour. Great thirst was noticed and a voracious appetite.

The specimen of urine which he passed in the office had a specific gravity of 1035, a trace of albumin, bile was present but not indican. Sugar by the copper test 6.2 per cent., by fermentation 6.4 per cent.; the elimination of urea was noticeably not relatively great, 0.99 per cent.

Two days later, having put him on his first visit of the sixth upon a diet which, while by no means starch free, was calculated to be bland and contain no particles to serve as physical irritants to the membrane, the quantity of urine for the twenty-four hours was reported as a little over three quarts, specific gravity 1034, sugar by copper and fermentation 6 per cent., urea 1.4 per cent. A Riegel test-meal taken three hours after ingestion showed normal amount, catarrhal mucus in considerable quantity, stained with blood. No free hydrochloric acid, and no lactic acid.

In this case, owing to business requirements of patient, the use of the alkaline lavage was not immediately instituted, but he was treated with resorcin and chloroform-water (one drachm of resorcin to four ounces of chloroform-water), a teaspoonful taken without water before meals, this formula being one of which I make large use in cases of catarrhal gastritis, independently of the presence of sugar.

He reported that the first night in place of rising every hour and passing enough urine to fill a slop-jar, he rose but once. The second night his sleep was unbroken and he has not been disturbed at night since this time for urination.

One week later, February 15th, the quantity for the twenty-four hours was four and three-quarter pints, specific gravity 1028, urea 1.08 per cent., sugar by the copper test 1.5 per cent. All excessive thirst had gone and his appetite was normal.

February 27th the urine showed a specific gravity of 1015, urea 1.35 per cent., sugar absent by the bismuth, copper and fermentation tests. Examinations were repeated March 7th, 14th, 21st, 28th, April 1st, 5th, 11th, 25th, 26th, May 9th, 19th, 31st, June 6th, 27th, July 5th, 16th, August 8th, September 19th, October 10th and November 7th, and sugar has not been found at any time. The specific gravity ranged from 1016 to 1020.

The last test-meal was taken April 28th, when the catarrhal process was found much reduced, there being now but a trace of mucus without the blood and

other evidences of intense inflammation, but free hydrochloric acid was still absent. He has pursued his business, though at my urgent insistence he has diminished somewhat the line of work undertaken—not enough to satisfy me, but still enough to make some positive gain.

Case XIV.—Mrs. C., a housekeeper, aged fifty-five years, is a well-nourished woman. She complains of weakness, loss of flesh, thirst and hunger, and easy fatigue. There has been no serious illness in the personal history, but for some years she has been much troubled with gastrointestinal disturbances, for some of which I have treated her, finding catarrhal gastritis the usual disturbance, with occasional involvement of the duodenum, slight icterus and constipation. She is now troubled with spastic constipation.

The patient shows exaggerated knee-jerks, slight tremor, occasional tachycardia and slight enlargement of the thyroid, though not marked enough to attract attention until the neck is palpated. Graefe's sign is present, Stellwag's and Moebius' signs are absent. There is no exophthalmos and the peripheral arteries are not thickened.

During my care of her previously (and I am informed by Dr. T. C. Martin, while she was under his care) no sugar was at any time found in the urine. A specimen examined October 28, 1902, the twenty-four hours' secretion being more than three quarts, showed large quantities of sugar, by the copper reduction test 8 per cent., and 7.8 per cent. by fermentation; there was no reaction for bile or indican, the specific gravity was 1038.

The test-meal showed good motor function of the stomach with positive reaction for free hydrochloric acid, but apparently in diminished proportions, while the scanty quantity obtained showed undigested meat fibres enveloped in tough clumpy mucus.

The patient was not put upon a standard diet, but four grains of benzosol t. i. d. and alkaline water were prescribed.

The diet included bread, mashed potatoes, corn-starch, arrow root and tapioca; the restrictions were principally abstinence from cane sugar, and irritating substances like seed coats and fibres and all raw fruits. Cold baths were also ordered. On November 3d the specimen of the twenty-four hours showed by Fehling's solution 2.8 per cent. of sugar, and by fermentation 2.3 per cent. On November 26th, the patient feeling very much better, there were two quarts of urine in twenty-four hours, and Fehling's solution gave 1.3 per cent., and fermentation 1.5 per cent.

On December 2d the specific gravity was 1016; no reaction was obtained for sugar by copper nor by Nylander's solution, nor in the several tests made on January 9th, 14th, 27th, March 9th and April 17th.

On May 7th, three hours after taking the Riegel test-meal, 15 c.c. of stomach contents were obtained, showing the following in three layers: the upper third was mucus with food residue, the reaction showing a total acidity of 66 c.c., of which 30 c.c. were free hydrochloric acid. The other physical findings remained the same. Although she has experienced considerable subjective

benefit from the use of cold sponge baths, the knee-jerks, tremor, tachycardia and Graefe's sign still remained unchanged.

The patient throughout this period has taken quantities of starchy food beyond the usual amount often indulged in by those who have had no trace of sugar in their urine.

On September 22, 1903, sugar was again found in large quantities in the urine, 5.6 per cent.—but there was neither thirst nor polyuria, and repeated examination throughout the year has shown the constant presence of sugar without polyuria, without thirst, without feeling of weakness.

October 1, 1904, she reported herself as never feeling so well, but on November 7th she came stating that within the past few weeks she has noticed a beginning of thirst, and in the specimen sent in on December 12th there was found 5.4 per cent. of sugar in the two quarts in the twenty-four hours.

Lavage was begun and immediately thereafter great subjective relief was experienced. The thirst which she was beginning to notice again has disappeared and the percentage of sugar decreased to 3.6 per cent. in the twenty-four hours' secretion. There is again present a considerable catarrhal gastritis with motor insufficiency.

In this case the slight exacerbation of the catarrhal gastritis is always found with the slight increase of thirst, and the relief is gained in the presence of a persistent excretion of sugar when the stomach condition is bettered by local treatment of the viscus, without change in diet or in any other respect.

Case XV.—Mr. H. has been under my care very frequently and has been a family patient of my father's for many years.

I had occasion to make urinary examinations in his case on January 23 and July 24, 1902, and in each specimen sugar was absent. In January he was suffering from a well-marked catarrhal icterus and at various times in the preceding years has presented the same evidences of obstruction of the bile-duct from simple inflammatory processes apparently excited by rapid overeating. The patient has suffered from eructations of gas and a sense of load and weight in the stomach after meals, and has, at various times, corresponding to the development of the duodenal catarrh, noticed the passage of clay-colored stools. There has never been ground for diagnosing gallstones. This patient has been unwilling to take a test-meal, and I have not strongly urged it upon him for various reasons such as obtain in general practice.

On December 8th, four and a half months after the last test of urine, he came to me complaining of some weakness, easy fatigue, and one week before he had noticed a suddenly increased thirst which had continued through the week. The examination of the urine was at once undertaken and a specific gravity of 1039 was noted with the positive reaction for bile.

Sugar was found in large quantities by Fehling's solution 8.4 per cent., by fermentation 8.5 per cent.

The meaning of findings were explained to him and he was put upon Vichy water, cautioned to withdraw sugar from his food and to diminish the amount of starch.

Knowing the difficulties of controlling this patient I did not think he would stand at all well the sudden withdrawal of all starchy foods.

The prescription in his case was the resorcin and chloroform-water as in the others.

The following day the excretion was over two quarts with a specific gravity of 1036, and gave a large quantity of sugar, 6.2 per cent. by Fehling's, and 6.4 per cent. by fermentation.

One week later the specific gravity was 1029, and the sugar was 3.3 per cent. On December 24th the twenty-four hours' secretion showed 0.83 per cent of sugar. On January 13th 0.2 per cent. of sugar was found, and on May 5th none was found by fermentation, the specific gravity being 1020, bile positive and urea 1.6 per cent.

The patient writes: "For four weeks I have eaten bread, meat, potatoes and fruits as usual in my life. Yesterday I ate freely of wheat cakes and maple syrup."

After some months of pursuing his dietary folly it was followed by the reappearance, but his previous easy relief made him discount the importance of the difficulty.

Case XVI.—Four years ago the patient, Mr. M., was for a year or more under my care, during which time he suffered from a catarrhal jaundice with accompanying catarrhal gastritis. During the year I made several examinations of the urine, and sugar was not found at any time.

On May 26, 1903, he again consulted me, stating that his physician in the town in which he lived had a week previously found sugar in his urine (but the examination was not made till the patient had been under treatment for some time). The duration of the excretion of sugar before coming was not less than one month, probably more.

The patient was slightly jaundiced, and thinking that he had a recurrence of his old difficulty, I used the stomach tube to ascertain the condition of the residue in the stomach and found a small quantity of catarrhal mucus with markedly free hydrochloric acid, not enough, however, for the quantitative tests.

Examination of the urine gave a specific gravity of 1026, albumin, bile, and sugar all present, indican negative, and hyaline casts with granules. The quantity of sugar was 6.2 per cent. The urea content was very low, only 0.67 per cent. being obtained by Squibb's method. The patient declined the test-meal, so that I was unable to report more definitely about this case with respect to the condition of the stomach. A twenty-four hours' collection of urine, from which a specimen was sent on May 28th, gave as a quantity two quarts, specific gravity 1134, albumin and bile positive, sugar 7 per cent., urea 1.2 per cent. No red reaction with ferric chlorid was obtained.

The patient was directed to take three drops of Fowler's solution three times a day after meals and drink Saratoga Vichy. He was cautioned to avoid the use of all sugar and starch, and four days later, after a rigorous exclusion of the sugar and starchy foods—*i. e.*, "standard diet"—the patient sent in a

secretion of twenty-four hours amounting to three pints, the specific gravity of which was 1007. Albumin, bile and sugar all present. It contained 2.7 per cent. of sugar. Mashed potatoes and a slice of bread were allowed with each meal, especial pains being taken to reduce all particles of food to a bland and non-irritating form, all high seasoning to be avoided, and rest after meals was advised. He was also allowed a small portion of corn-starch and manioca. Resorcin and chloroform-water were prescribed.

On June 8th the amount of urine obtained was one quart, the specific gravity 1026, albumin and sugar were positive, the sugar being 0.62 per cent. "The patient states that he has been eating a ton of mashed potatoes a day and a little bread."

By his rather generous estimate he meant that he had eaten three times a day a quantity of mashed potatoes about equal to a double handful. Peas and beans mashed through a sieve were added to the diet. On June 18th the quantity of urine in twenty-four hours was forty ounces and the specific gravity 1022. It contained a mere trace of albumin, and no sugar was present. Similar tests were made on June 22d, 26th, July 2d, and 6th and no sugar was found.

He has eaten of mashed potatoes and he has also taken corn-starch, peas, beans, tomatoes, onions, manioca, and I suggested the use of apple tapioca pudding and similar preparations.

On July 8th no sugar was found nor on July 13th, 21st, and 25th, nor in the several examinations since then.

Case XVII.—Mrs. W., aged fifty-five years, a widow, colored. Had malaria seven years ago, and four years ago is said to have had three strokes of apoplexy, very slight. Directly following these attacks began to be very thirsty, voracious appetite; she also passed great quantites of urine, which kept her feeling weak, and she lost fifty pounds in weight. This continued for two years, then she improved so that her desire for water and food diminished and she returned to work for one year. In July,1904, a return of the symptoms, thirst, appetite and increase of urine; has had pruritus; at present, April 22d, she is very thin, otherwise no abnormal physical findings.

Before entering the hospital she was passing four quarts of urine per day, and during her stay in the hospital, on lavage with alkali, there has been a quantity varying from 1000 to 2000 c.c. of urine, with an average percentage of sugar of 3.5 per cent. Her thirst and hunger have been markedly relieved, and her strength has also been much improved. The standard diet did not materially affect the percentage of sugar, but the patient expresses great relief from the lavage.

The test-meal in this case, taken May 1, 1905, gave 40 c.c. of stomach contents, which separated into two layers, nearly all of which was tough catarrhal mucus. Hydrochloric acid was absent, lactic acid present, total acidity.

Case XVIII.—Mr. H., aged forty-two years, a manufacturer, referred by Dr. W. A. Knowlton. For fifteen years has had some digestive disturbance,

otherwise well save for la grippe. In June, 1904, began to be very thirsty, urinated frequently, and in October noticed he had lost twenty-five pounds. He was put upon the usual antidiabetic diet, but in March developed a jaundice which has been persistent, though at this writing is improved.

The quantity of urine in twenty-four hours had never been measured till this time, when, although it was much reduced, it was still six to seven quarts a day, the percentage of sugar 4.1 per cent., and heavily loaded with bile.

The Ewald test-meal gave 200 c.c. of stomach contents, which separated into two layers, of which 160 c.c., top layer, was clear liquid and 40 c.c. food residue, the free hydrochloric acid 36 c.c., and total acidity 80 c.c.

The standard diet is not well borne by this patient and can not be persisted in. Two days' trial does not reduce the percentage of sugar. Under lavage and rest in bed, hot applications and enemata the patient has lost his thirst and excessive hunger; is now passing about three pints of urine per day with from 2 per cent. to 2.5 per cent. of sugar. There has been distinct improvement in the condition of the patient and he expresses great relief from the practice of lavage.

Case XIX.—The last case which I shall read to-day is that of a man who came to my office October 6, 1904. A specimen passed in the office showed 3.9 per cent. of sugar.

The patient and his physician, Dr. Morton, stated that for nearly two years he had an excretion of sugar, the last six months with a very great polyuria and a loss of flesh of fifty pounds—weighing now 240 pounds.

This man was one of great strength and size, a market man, who had never measured the quantity of urine for twenty-four hours, but who reported that for several months each night between 9 P.M. and 3.30 A.M., when he rose for the day's work, he passed on an average fourteen quarts of urine. During the day his excretion was of large quantities of urine every half-hour, so that it is no exaggeration to state that his urination exceeded thirty quarts per day.

His thirst was correspondingly enormous. When coming to my office the urine contained a considerable quantity of albumin, and he had had for five days a marked amaurosis with a marked *retinitis albuminurica*. He had been unable to distinguish light from darkness for three days, but in the last two days he had a considerable betterment of sight.

I wanted him to go at once to the hospital, but he felt he must go home that night to consider the idea. He was taken that evening with uremic convulsions, for which I was consulted by telephone, and prescribed hot packs and that he be taken to the hospital at once if possible. He was taken there directly and the packs were started at once. The first urine passed was nearly solid with albumin, containing no sugar, the next specimen containing 2.4 per cent.

Lavage was begun in connection with the packs and the second day his thirst had entirely disappeared, though sugar was still present.

The test-meal taken October 9, 1904, gave 250 c.c. of stomach contents, the gross appearance of which was large quantities of undigested food which did not separate into layers, with much mucus in the mass.

The free hydrochloric acid was 18 c.c., the total acidity 54 c.c. Microscopically there were present mucus, starch, blood cells and yeast.

October 8th, the quantity of urine was 500 c.c., sugar 0.9 per cent.

10*th*, 930 c.c., 0.725 per cent. of sugar.

11*th*, 1020 c.c., 0.4 per cent. of sugar.

12*th*, 1200 c.c., 0.28 per cent. of sugar.

13*th*, 900 c.c., 0.37 per cent. of sugar.

15*th*, sugar absent.

In the specimens which have been brought to the office to date there has been no trace of sugar.

This case is a most gratifying one as to his present condition. Its interpretation is, of course, open to the uncertainty as to the cause of the disappearance of the sugar, from the fact that in some cases of diabetes the development of a nephritis is attended with the disappearance of sugar; but I have thought this case might well be included in the present study, as there are absent cardiac hypertrophy, or edemas, to indicate the establishment of a chronic nephritis.

The duration of his glycosuria, the enormous excretion of urine, often exceeding fourteen quarts in a night, his voracious appetite and corresponding thirst, with loss of flesh and weight from one year ago, weighing 296 pounds, to February 3, 1905, when he weighed 182 pounds, with his prompt recovery from a most threatening condition and with a total disappearance of sugar from the urine, the quantity averaging one quart per day, mark the case as one of unusual type and interest.

When these nineteen cases are examined as to the relation between the stomach disorder and the diabetes, we find that of the nineteen, fourteen gave evident histories of previous dyspeptic trouble, one of alcoholism without dyspepsia noted, three slight indigestion, and only two stated a complete freedom from dyspeptic disturbance.

The age of these patients ranges from two at fifteen to one at seventy-three. Six of the cases are twenty-three or younger, one is twenty-seven, and one twenty-eight. All the others are over forty.

As to the duration of the glycosuria, nine of the nineteen are known to have been diabetic for years, seven known to have been diabetic for months, one possibly for a month, while in two the period is thought to have been from one to six weeks; and from

these considerations, as well as from the clinical history while under observation, all are fairly to be excluded from the range of alimentary glycosuria.

Among them are cases of the severest type, as well as of the milder forms.

With reference to the condition of the stomach sixteen show abundant catarrhal mucus, clumpy, sago-grain-like in the contents of the stomach; two do not show this catarrhal process, and from one, owing to age and disinclination, no test-meal was obtained.

As to motor function, ten show a considerable failure, and of the eighteen cases the secretion of hydrochloric acid in eight is increased; seven show normal proportions, three show less than normal or absent.

In the three cases showing less than normal, Case XI., with a markedly catarrhal process and an alcoholic, with a considerable amount of pus, may well have been in the acute development just at the stage in which the acid had recently disappeared.

Case XIII. shows an active catarrhal process, which often inhibits the production of acid.

The analysis of these cases confirms the previous investigators as to the absence of any definite relation between the presence or absence of free hydrochloric acid and the excretion of sugar.

Of the nineteen cases all but two show definitely active catarrhal processes, and in every case of the nineteen has there been marked subjective benefit—gain in strength, weight, freedom from thirst, and polyuria—gained by direct attention to the catarrhal process, and in two cases, without presently existing catarrh, there has been some measure of benefit.

The most striking influence has been observed on the polyuria and thirst. In some cases the percentage of sugar has undergone no change, but there has been in these cases a great reduction of the total excretion of sugar per day, owing to the great change in the quantity of urine excreted, and the clinical course of this group of diabetics has been much more favorable under direct treatment of the stomach than without it. Moreover, the cessation of this treatment has been followed by the recurrence of the difficulty with prompt relief on resuming the treatment directed to the catarrhal process.

In most of these cases lavage formed an important part of the treatment, using antiseptic and alkaline solutions. In a few lavage was not instituted, but remedies and diet adapted more to the catarrhal gastritis than to the diabetes was followed by prompt relief and disappearance of the sugar. These were cases of recent development in whom the catarrhal process also was freshly active. Of the marked influence of lavage, Cases II. and III. are of especial interest because the observations were under favorable conditions, and show in the charts the marked additional benefit from lavage, done twice daily, as contrasted with the results obtained from its performance once a day, all other conditions remaining the same.

I should here state that instead of the siphon used in the upright position for cleansing the stomach I routinely use the Politzer bulbs, the patient being in the reclining position, and also make use of free manipulation of the entire area of the stomach, believing that by so doing I secure a more thorough cleansing and more direct application of the drug than is possible in the customary procedure.

Pending the further study to explain these results, I do not desire to anticipate later findings, but that much may be accomplished for the comfort and relief of many diabetics from direct attention to the condition of the stomach seems to be established in these cases.

In this connection it is also proper to suggest that the use of alkaline waters, like Vichy and Carlsbad, which have been helpful in a great number of patients, may receive a possible explanation of their effect.

So far as lavage removes from the stomach substances capable of irritating the nerve terminations it becomes possible to see how at least a part of the favorable influence of opium in this disorder is exerted, as this drug diminishes the irritability of the nerves concerned.

So far it has been difficult to directly connect the work of Pawlow and his assistants and of Bayliss and Starling with these observations, but of the clinical advantage in the treatment of diabetes to be derived from attending directly to the disorders of the stomach digestion which have been thought to be simply results of the diabetic state, I believe careful trial by the methods indicated will prove convincing.

DISCUSSION.

Dr. Tyson: These observations seem to me of very great importance. I confess that in my experience with diabetes mellitus I have not especially noticed a very frequent association of active gastric disturbance or symptoms which would call one's attention to the stomach as deranged in function. On the other hand, we well know in a large number of these cases the stomach functions are especially well carried out. Can it be that the efficacy of Fowler's solution, which I think is undoubted in the treatment of diabetes mellitus, and which has not heretofore been easily explainable, is due to some action of this drug upon the stomach function? It appears to me also not impossible, too, that acetone and diacetic acid formation may be the result more frequently than we suppose of a catarrhal gastritis, and I should like to know from Dr. Sawyer whether he has attempted to treat diabetic coma by lavage. I would expect from what he said of the effect of lavage in the treatment of uncomplicated diabetes mellitus that it might be useful in the treatment of diabetic coma.

Dr. Kelly: I have been so much interested in Dr. Sawyer's remarks that I venture to make one or two queries: (1) whether he regards the cases that he has reported as examples of true diabetes; (2) if so, whether he has formed any conception of the pathologic processes at work and what they are; (3) what effect he believes lavage exerts or can exert upon the disturbed metabolism commonly believed to be the basis of diabetes. These I think are important queries in connection with Dr. Sawyer's paper and should be elucidated. If, however, we can improve our diabetic patients, as Dr. Sawyer suggests, we shall have gained a valuable addition to our therapeutic procedures; but it is, nevertheless, interesting to inquire how this improvement may be brought about.

Dr. Cohen: In many cases of chronic glycosuria, as I prefer to call the condition in order not to commit myself, I have observed recurrence or increase of the excretion of sugar coincidently with the onset of septic conditions in the intestine as manifested by diarrhea, flatulence, etc., and disappearance or diminution of the sugar under lavage of the intestine and the administration of intestinal antiseptics. That has been so frequent an occurrence with me as no longer to excite any special interest. I should like to ask Dr. Sawyer for some additional information in regard to the effect of his treatment on constituents of the urine other than glucose. Does it diminish the acidity of the urine? Does it increase or diminish the quantity or ratio of urea and total nitrogen? Does it alter the quantity or ratio of ethereal and other sulphates. I have long been in the habit of ordering for chronic diabetics and glycosurics the constant use of sodium bicarbonate or some other alkaline

salt as a preventive of acid intoxication, and I belive that by such constant alkaline treatment, keeping the urines neutral to litmus paper, alkaline to phenolphthalin, we do in many cases avert the occurrence of coma. This is better than to wait for dangerous symptoms, and then resort to alkaline hypodermoclysis or venous infusion. Has Dr. Sawyer attributed any part of his good results to the alkalinity of the lavage solutions?

Dr. Sawyer: I have been very much gratified at the interest the gentlemen showed. I do not think I can answer all these questions without trespassing too much on your time, but first as to the efficiency of drugs of which Dr. Tyson spoke. In my abstract these have been omitted because it was impossible to give any exhaustive list of them in the space given me. I believe that Vichy and Carslbad water are, by reason of being alkaline, very beneficial. I think that they serve as a sort of inefficient lavage, and that they accomplish some good in that way. They are known to be of distinct value in catarrhal processes. I think that the Carlsbad salt may act not altogether without some such influence as this. Then the alkalies are certainly of great value. I have had only one case of diabetic coma to treat. This young man, who had been out on a prolonged alcoholic indulgence, was certainly in a most unfavorable condition. I was not able to affect favorably his coma. That the use of alkali cures all case of coma we have not found. As to this being true diabetes, I would like to ask what we are to consider true diabetes? The symptomatology has been excretion of sugar in constant continued recognized quantities. It has been looked upon as a characteristic of the diabetic that there is a continual excretion of sugar; that there is polyuria, thirst, emaciation; that there is weakness, and in all these particulars all of them are to be classed as diabetics, and when tested by the trial of a standard diet extending over periods of weeks, there are no cases which will show much more clearly than do some of these cases the existence of diabetes. As to the presence of sugar in the blood, that is not a matter of easy clinical research. The test of Williamson, the test of Ringer, the color tests, Congo red and methylene blue are not to be looked upon as satisfactory to our physiologists.

In the treatment of these cases I have taken routinely these blood drops and have found these reactions present.

Further, as to the question as to the nature of diabetes, I carefully avoided in my paper speaking of the etiology of diabetes. In my remarks I carefully made the statement that in the course of diabetes there was advantage in treating the stomach. I do not wish to commit myself or prejudice myself beyond that form. There is work going on which is necessary, which is perhaps to be fruitful, but it may be absolutely without result. So far I present the one claim of clinical advantage in diabetics treated in this fashion.

Regarding asepsis in the intestinal canal, I think it is quite important in diabetes to treat such conditions. I think the intestinal canal is best treated by guarding the stomach, by seeing that food entering the stomach is not

destroyed or interfered with by the initial error in the stomach, and perhaps in these cases gain this advantage. McCaskey has reported several such cases.

With reference to the constitution of the urine treated in this fashion it has not been possible for us in the material, which is almost altogether a private one, to carry out these experiments. We have not been able to carry them to the point of completion that would warrant their quotation. We have found that urine six to ten quarts, and in one case of over thirty quarts, with a specific gravity of 1040 to 1038, has been reduced to two quarts, three quarts and 1030 to 1038, and the inference is irresistible that the very considerable gain is made by diminishing the destructive metabolism, of which we look upon the urea as a clinical index. There is a considerable gain in this respect.

I think alkaline solutions are valuable. It neutralizes the acid, which is a minor consideration. Its value as alkali is as a solvent of mucus, cleansing thoroughly. With the use of Politzer bulbs no alkali is left in the stomach. This is not an administration of alkali, but a washing with alkali.

All through I make use of Vichy and other medicinal measures. This lavage does not interfere with the use of adjuvants. I believe with it we may give more starch, nourish our patients better and see them gain more than we could without treating in this way.

CALCAREOUS DEGENERATION.[1]

By OSKAR KLOTZ,

DEMONSTRATOR AND LATE GOVERNORS' FELLOW IN PATHOLOGY, MC GILL UNIVERSITY, MONTREAL.

	PAGE
Introduction	471
Staining Methods	475
Calcium and calcium compounds	475
Fats and fatty compounds	477
Chemical Methods	480
The determination of soaps	480
The Process of Deposit of Calcium Salts in Bone	481
In normal bone	481
Pathological bone formation	482
The Process of Deposit of Calcareous Salts under Pathological Conditions	483
In the arterial wall	483
Calcareous infiltration of thickened pleura	488
Calcified fibromata	489
Calcareous infiltration of ovarian and broad ligament cysts	490
Calcareous tuberculous nodules	490
Pancreatic fat necrosis	491
On the Presence of Soaps in the Organism under Physiological Conditions	493
The Presence of Soaps in the Organism under Pathological Conditions	495
The Existence of a Compound of Soaps with Albumin	497
The chemical isolation of soaps from pus	497
The Experimental Production of Calcification	498
In capsules containing fats and fatty acids	498
Experimental calcification in the kidney	499
Experimental calcification of muscle fibres	503
Experimental fat necrosis	504
On the Source of the Fat in the Degenerated Cells	504
Conclusions	507
Bibliography	511

[1] This study was begun while the writer was Governors' Fellow in Pathology of McGill University, and has been continued and completed under a grant from the Rockefeller Institute for Medical Research.

INTRODUCTION.

It is a well-known fact and a not uncommon occurrence that the interest in certain subjects or lines of thought fluctuates widely; we are ever too ready, when we think we have obtained an explanation of a certain phenomenon, to take much for granted and allow our enthusiasm to lapse. Such has been the case in the study of pathological calcification, which has gone through several periods of new theories and rest.

Notwithstanding these theories, in reviewing the literature concerning calcareous degeneration or calcification, one is struck with the dearth of actual facts that are set forth upon which those theories are based. In truth, the labor that has been spent in the actual study of the *process* has not been extensive and it is confined to a few papers in the last decade. There have been many who have reported the occurrence of calcareous degeneration of diverse tissues and have even gone minutely into the chemical nature of the organic salts present, but here the study has ended. Regarding the existence of pathological calcification we have abundant data, as to the process of calcification we know little.

Indeed, calcification is one of the commonest pathological conditions noted by the older writers, especially that occurring in the arteries and in fibromata of the uterus. Not infrequently the change in the arteries is spoken of as appearing "partly fatty and partly earthy." No doubt reference was made to the yellow atheromatous areas overlying calcareous plaques in the arterial wall. Not until Virchow, in 1858, asserted that inorganic salts were deposited in supersaturated solutions of the same and that the deposit of calcium was of this nature was there any discussion on the subject. Virchow held that calcareous deposits were chiefly found in old age and in diseases causing wasting of the bony framework, and that in this state calcium was dissolved out from the osseous system, and, on account of the too concentrated solution of calcium salts in the blood, these were laid down elsewhere as metastatic deposits. In

this way he explained the common occurrence in old people of calcareous plaques in the arteries.

Some years later von Recklinghausen reported the studies he had made upon the degenerations. He pointed out that calcium deposits result partly in tissues which are well supplied with tissue fluid, but also in tissues poorly supplied. When blood or tissue fluids are saturated with calcium salts, due to repeated breaking down of bony structures, he noted a secondary incrustation of the lung and kidney tissue. But there were other cases in which, as in fibroids and phleboliths, calcification proceeded under normal conditions of the calcium content of the blood. Von Recklinghausen looked on the processes of ossification and petrification as similar chemically, though differing biologically, in that the former took place in active and living cells, the latter in degenerating or dead tissues. He held that the factors governing calcification were: (1) the separation of sparingly soluble lime salts, (2) the existence of these substances in excess in the fluids, and (3) the presence of a foreign body which acts as a nucleus.

These factors would be of weight in considering fluids outside the body but not within. The lime salts in the tissue fluids are not found in excess during calcification and the common salts of lime found in the tissue fluids are very soluble. The deposit of calcareous plaques in the serous membranes and in the arterial walls he considered under ossification and as distinct from calcification.

Lancereaux's views were very similar to those of von Recklinghausen, though he attributed the supersaturation of lime salts in the blood to a hindrance of the excretion of these salts by the urine, and found them accumulated in the pyramids of the kidney and the mucosa of the stomach and intestines.

Thus it was that up to the time of Litten's ingenious experiments (1881) the theory of the excess of lime salts in the blood was accepted as explaining calcareous degeneration. No note was taken of the predilection of certain tissues for this deposit of lime, except that dead or dying tissues were regarded as a nucleus about which the carbonate and phosphate of calcium

would crystallize. With Litten's studies—which will be discussed more fully later—a new theory was raised which superseded that inaugurated by Virchow, and this up to the present time has been the accepted explanation of calcification in the text-books. With the arrival of Litten's work many followed in his footsteps, in the main supporting his views, although some have disagreed with him. The prevalent view, based on that of Litten, is briefly (dealing particularly with the cases of calcareous degeneration in the kidneys) that one or more irritants act on certain tubules in the kidney through which these irritants are excreted, and during their passage through the kidney cells so injure the tubular epithelium that a degeneration of the cell protoplasm occurs, and that this degenerated cell protoplasm has an affinity for, and fixes as an insoluble compound, the calcium salts brought to it by the lymph and blood. Such, it is maintained, are the essentials for the deposit of calcium salts, and especially is it pointed out that a coagulation necrosis of the renal epithelium is a necessary stage in the process.

This view has been generally accepted, and yet it is noteworthy that no one has proved that outside the body there is to be obtained the formation, even temporarily, of compounds of lime and any form of proteids.[1] The present investigation was undertaken, in the first place, to determine with what organic substance present in degenerating tissues could be shown that lime salts entered into combination. It was in repeating Litten's and von Kossa's experiments and in studying also the changes occurring within celloidin capsules containing various substances and introduced into the peritoneal cavity that indications were gained leading to the results about to be detailed. It was first undertaken to produce, experimentally, calcification of the kidney and other tissues and to study the successive changes to be noted in these. The rabbit was most frequently used in these experiments, partly on account of the normally high calcium

[1] The nearest approach to such formation with which we are acquainted is the conversion of "soluble casein" into a curd by the addition of calcium chloride (vide Halliburton in Schäfer's *Physiology*, vol. i. p 135). This curd is supposed, but has not been definitely proved, to be a *calcium caseate*.

content of the blood and partly because these animals stand various operations very well. But in addition many calcified tissues from the human body were studied, especially the process in connection with arteriosclerosis, and, as will be detailed, not a few experiments of other nature were made during the course of the investigation.

In studying the calcareous degenerations the tissues were subjected to a series of tests as to the staining qualities and the chemical nature of the material. From all the experimental work on animals and the analyses of human degenerating tissues there was always one conclusion arrived at—namely, that calcareous degeneration is preceded or accompanied by deposits of a soapy material. This soap exists in chronically inflamed tissues in advance of the deposit of lime, or if the lime is already to be found in the tissues, the soap appears in the peripheral zone of the calcareous infiltration. Moreover, it would seem that, with the first deposit of soap, calcium salts are immediately attracted to it from the body fluids. Such progressive calcareous deposits are marked by the appearance in the periphery of groups of granules, some of which are found to react for both calcium and soap, others for soap only—that is, some of the soap deposit has been converted into a compound containing calcium—in other words, calcium exists in the recently calcified areas as calcium soap.

That this calcium soap does not continue to exist as such was noted in old calcified fibroids and other tumors. In these it was seen that, except in the advancing border of calcification, the dense calcareous deposits are composed chiefly of calcium carbonate and calcium phosphate with no soap in its substance. It would seem here that the fatty acid moiety of the calcium soap had been replaced by the stronger phosphoric and carbonic acids to form the more stable compounds.

This is, in brief, the trend of the paper.

Before proceeding with the description of the work I wish to extend to Professor Adami my best thanks for the supervision of the entire work, and for his unfailing help and the many suggestions which have been of great aid to me during the course of this and other researches.

STAINING METHODS.

Calcium and Calcium Compounds. As a routine all specimens were stained with hematoxylin and eosin. These stained specimens gave the general character of the section, and, moreover, the presence of calcium salts, when in fair amounts, was indicated by the appearance of fine blue-black, dust-like granules, which stained darker than other portions of the tissue and were easily recognized. The hematoxylin will, however, only stain calcified areas when calcium salts are present in very fair quantities. Slight amounts are unrecognizable by this stain.

To demonstrate calcium salts in tissues we have two other methods, one of which was of the highest service in my hands. If tissues containing lime salts be treated for five minutes with a solution of pyrogallic acid (1:40 in water), to which 1 per cent. of sodium hydrate has been added, the lime salts will be stained a dark-seal brown while the remaining tissue appears a light-yellow color. Except in tissues where large quantities of lime salts are present the stain is unsatisfactory, just as in many cases which show the presence of calcium salts with the following method the pyrogallic acid treatment gave no results. The most satisfactory method we have used is that recommended by von Kossa—namely, the treatment of sections with a 5 per cent. aqueous solution of silver nitrate. This solution picks out the most minute quantities of calcium by depositing an intense black precipitate in its place. The sections were immersed in the silver solution for from three to twelve hours, then washed in distilled water and mounted in the usual way in Canada balsam. As the silver treatment of sections consists of an impregnation and precipitate in the tissues and not a stain, we obtain a much exaggerated picture of the actual quantity of lime salts present. However, this is of all the more service when minute quantities of earthy salts exist, and the method is not proposed as affording a quantitative measure.

As was pointed out by von Kossa, the blackening produced by the treatment of sections with silver nitrate is due to the production of silver phosphate, which blackens in the presence of light;

hence it would seem that a precipitation of silver is only obtained in the presence of a phosphate. The calcium deposit in the tissues exist, however, as both a carbonate and a phosphate, principally the latter, and this experiment would only lead us to detect the insoluble calcium phosphate. However, when sections containing calcium carbonate are treated for many hours with silver nitrate a certain portion of the two salts interact, so that the calcium carbonate granules become coated with a deposit of silver carbonate, which in sunlight gives off carbon dioxide, leaving the black silver oxide; or we can hasten the stage of blackening when some silver carbonate has formed by first thoroughly washing the specimen in distilled water and then treating it with a dilute soluble sulphide.

There is, however, I would point out, a means whereby the calcium existing in any favorable combination in the tissues can be demonstrated by the silver-nitrate method; and this consists in first converting calcium salts into the chromate by means of potassium chromate and then replacing the calcium by the silver, thus obtaining the silver chromate, which blackens on exposure to sunlight. Under ordinary conditions the calcium chromate is soluble in water, but when tissues containing calcium are acted on in the cold we find that the calcium chromate does not leave them, and on further treating them with silver nitrate the red silver chromate is seen to become deposited in their sites. The use of silver nitrate in these impregnation tests, we have found, is facilitated by acidulating it with acetic acid. This same method demonstrates calcium when combined with fatty acids to form soaps.

I would point out that these microchemical tests for calcium do not demonstrate the actual calcium salts, but by replacement we demonstrate their presence and location with blackened silver salts.

Virchow and Halva have both examined calcareous nodules by chemical analyses, demonstrating the presence of both phosphate and carbonate of lime. However, they point out that the phosphate is much in excess, while Chiari found only phosphatic salts in the calcified nodules examined by him.

This method of staining lime salts with silver nitrate gave beautiful pictures in all of the tissues examined. Especially was this true of the sections of experimental calcification of the renal tubules. (See Fig. 2.) It is true that the metals mercury, copper and lead will give a black precipitate in tissues with silver nitrate, but these can be excluded in these cases when other evidences are given of the identity of the calcium.

However, in the experimental production of calcium deposits in the kidney we have to deal with another factor not often met with in the slowly forming calcareous nodules. In the former we are inducing a sudden change by means of chemical or mechanical reagents, and this has an effect on the general metabolism. Especially is this so in the inoculation of animals with such poisons as corrosive sublimate, lead acetate or copper sulphate. Here, besides acting directly on the kidney tissue, we produce an hæmolysis of the red blood cells, and thus, occasionally depending on the strength of the inoculation, we find an iron deposit in those same convoluted tubules which are the seat of calcareous degeneration. Similar though less amounts of iron can be demonstrated in the liver, but that the presence of iron in the kidney is not the cause of the silver deposit is to be ascertained from the fact that no calcium reaction results in the liver. The iron in both instances is detected by the Prussian-blue test. Attention has already been called by Gierke to the occasional presence of iron in specimens of pathological calcification.

In the routine examination of aortas we were struck by the frequency of stainable calcium salts found in either the media or intima where no lesion was suspected from the macroscopical or ordinary microscopical examination.

Fats and Fatty Compounds. For the detection of fats, fatty acids and soaps I found that Sudan III. gave the most satisfactory results. I have also used Scharlach R., which is a very closely allied stain to Sudan III., but found a difficulty in the employment of it, as the stain precipitates very readily in its crystalline form into the tissues. Scharlach R. is the more intense, but cannot be used in saturated solutions. Osmic acid impregnation of tissues to demonstrate fats is of more limited

use, as we know that only the oleic acid and olein are blackened by it, while stearic and palmitic acids, with their respective fats, are left untouched. Hence in this work, outside of making comparisons of the quantities of olein or oleic acid with the total quantities of fats and fatty acids, sections were stained with Sudan III. Osmic acid was used only very occasionally. The nature of Sudan III. and Scharlach R. is such that they are insoluble in water, but are soluble in alcohol, chloroform, ether. fats, fatty acids and soaps. A saturated solution of the stain is readily obtained in 70 per cent. alcohol, and as the fats, fatty acids and soaps are more ready solvents of it than is 70 per cent. alcohol, fat in sections treated with a saturated solution of Sudan III. will pick out the stain, while the rest of the tissue remains untouched. Our sections were usually stained twelve to twenty-four hours in the cold. (See Figs. 1 and 4.)

Hence, in Sudan III. we have a stain which will differentiate fats, fatty acids and soaps from other products in tissues. That soaps are ready solvents for Sudan III. is readily demonstrated by making a concentrated watery solution of a soap and then adding the powdered Sudan III. The resultant mixture is a clear, deep-red solution, which can be filtered and further diluted. Such a stained, though highly dilute, solution when evaporated on a slide gives a pinkish-yellow color, which is distinct from the golden-red staining of neutral fat. Fat particles, even when emulsified to fine droplets, retain this intense golden-red appearance. The difference between the Sudan III. fat stain and Sudan III. soap stain is quite readily recognizable, so that the two can be detected in tissues. It is more difficult to distinguish the neutral fats from the fatty acids in stained smears under the microscope, though olein appears as stained oil globules distributed over the slide, which are easily picked out. These latter can be further differentiated by treatment with osmic acid.

It is to be noted that fatty acids as such are infrequent in the tissues, except in the case of dead tissues, such as gangrenous areas and pus, or as in the process of splitting up of fats in what are termed fat necroses. It is obvious that living tissues

do not pick up fatty acids unless, according to Fischler, it be leukocytes, in which we can at times demonstrate fatty particles in the cytoplasm and show the vacuoles about the particles to be of acid reaction.

Fischler is most emphatic in his assertion that Sudan III. is soluble in soap solutions, and the color produced on solution distinguishes this substance from the fat when stained in the same way; or, in other words, that fat and soap granules are to be differentiated on stained tissues. My results wholly confirm these statements. He states further that soap, when stained with Sudan III. and then treated with 70 per cent. alcohol immediately loses its color, the dye being taken up by the alcohol. This I cannot wholly confirm.

The statement is true of soap preparations in the test tube, but, as we shall see later, soaps present in the tissues do not dissolve so readily in weak alcohols; hence, they retain the stain after this treatment. As will be pointed out, these intracellular soaps do not exist as a free product, but form combinations with albumin with coincident alterations in reaction.

Calcium soaps are also stained by Sudan III., giving color reactions similar to those of potassium and sodium soaps. Calcium soaps, appearing in the tissues as a new deposit in which there is no excess of free calcium salts, are not distinguishable from other soaps; but when a portion of the calcium is freed and deposited either as carbonate or phosphate we find among the Sudan III. stained soap granules other (crystalline) bodies, highly refractile and not absorbing the stain. The latter granules, it is found, will precipitate with silver-nitrate solutions. In tissues, therefore, it is possible to treat the sections first with Sudan III. and later with silver nitrate, demonstrating the presence of soap granules, and also showing among these free calcium salts not associated with fats.

Some might be skeptical regarding the ability to distinguish the finest fat particles from the granules of soap stained in sections. Such skepticism we can override by another method. If the material be cut by the freezing microtome, the sections quickly dehydrated in 70 per cent. alcohol, then washed with

petroleum ether, the tissue may be rid of all the microscopical fat. If now soaps be present the soap reaction with Sudan III. will still persist. I do not wish to say that the ultimate fat is removed from the tissue, but all the stainable fat is taken out and the petroleum ether has been without action on the soaps. Rosenfeld and Dormeyer have pointed out that tissues which do not show fat microscopically when washed with ether or petroleum ether still contain a considerable quantity of fat present within the cells; but the combined fats of this order give no reaction with Sudan III.; they may be neglected in this regard. Here it may be noted that even after decalcified tissues have been prepared in the usual method for cutting in paraffin by dehydrating in absolute alcohol and clearing with xylol, sections will still stain faintly with Sudan III. in the regions of active calcification. I cannot but believe that in such cases we have to deal with soaps rendered less soluble by their combination with albumins. (See p. 499.)

CHEMICAL METHODS.

The Determination of Soaps. In our first experiments the method of Hoppe-Seyler was employed. The tissue under examination was finely ground up and extracted with boiling absolute alcohol. From the filtrate, evaporated to dryness, fats were later removed by ether or petroleum ether, and the residue was demonstrated to contain sodium and potassium soaps, along with small quantities of calcium soap. The residue, on treatment with mineral acids, yielded stainable fatty acids, all dissolving in water. The sodium and potassium soaps were precipitated with calcium chloride. As calcium soaps are so slightly soluble in alcohol, only small quantities of them were thus obtained, and we had to rely on the flame test to demonstrate the calcium present.

The use of this method of hot alcohol for the extraction leaves it possible, perhaps, that a small amount of neutral fat may be converted into soap by means of the alkalies present in the tissues. As I was, however, dealing with calcified tissues, such as fibromata of the uterus, from which all the surrounding

superfluous tissue had been removed, and which were then washed with distilled water, I can hardly believe that sufficient sodium or potassium remained in the tissue to give rise to the formation of soluble soaps.

To obviate this possibility of error the method was given up and the fats were extracted without the use of heat. After the material had been finely chopped it was dried over sulphuric acid and then extracted with petroleum ether in many relays, the powdering of the tissue being undertaken between each treatment with fresh petroleum ether. Dormeyer is very emphatic in his assertions that this method of treating tissues with ether, even when carried on for a long time, does not remove the last trace of neutral fats contained within the cell membrane. He prefers to digest with pepsin and 0.5 per cent. hydrochloric acid solution, and thus break up all the cell bodies, whereby he claims to obtain 8.5 per cent. more of fat.

As the analyses here undertaken were not of a quantitative but only of a qualitative nature, these minute estimations are of no bearing. However, the gross fats being once removed, the powdered residue was treated with hot acid alcohol to dissolve out the soaps (which had been unaffected by the petroleum ether) and a filtrate obtained. From the filtrate the soaps were precipitated with acid calcium-phosphate solution, filtered off and washed with ether. In tissues actively undergoing calcification this residue was obtained in fair quantity—in fact, in greater quantity than in densely calcified tumors in which the amount of the calcium salt was altogether out of proportion to the fatty acid. The alcoholic extract of the residue, after treatment with ether and petroleum ether, yielded small quantities of calcium soap, which we must remember is only very slightly soluble in absolute alcohol.

THE PROCESS OF DEPOSIT OF CALCIUM SALTS IN BONE.

In Normal Bone.· In the above description of the methods employed I have had to refer to the results obtained, and, if only in a general way, I have indicated that, in tissues undergoing calcification, fats, soaps and insoluble calcium salts are

found associated in varying proportions, according to the stage of the process. We will now turn to a more detailed study of the process and first consider whether under normal conditions—when calcium salts are laid down in bone—there is to be made out this same association; whether, in short, ossification and pathological calcification are processes of the same order.

The phalangeal bone of an infant six days old was examined by sectioning on the freezing microtome and staining with Sudan III. The head of the bone was cartilaginous with a center of ossification within it. The sections were allowed to stain for eighteen hours, but at the end of this time did not take the Sudan III. stain in any part. Both the cancellous and the compact bone were devoid of anything resembling fats, fatty acids or soaps. The femur of a fetal guinea-pig was next sectioned and treated in the same way and with like results; that is, we found that in normal-growing bone there appears to be no stage in which fatty substances play any part in the deposition of the lime salts, and we are led to believe that this laying down of calcium salts in the bone is a secretory process on the part of the osteoblasts. Again, in sections of decalcified skull bone we found the matrix entirely devoid of microscopic fatty substance. The bone corpuscles, or lacunæ, remained unstained with Sudan III.; nevertheless there was some neutral fat lining the Haversian canals and surrounding the contained bloodvessels. Thus we conclude that *the process of calcification in normal-growing bone is a distinct process in which the specific cells of the part play the chief role in laying down the calcium salts.* There was nothing in the stained tissue which would lead us to believe that there is any connection between fatty substances and the advancing bone formation at the epiphyseal line.

Pathological Bone Formation. What is true with reference to normal bone was found to obtain also in new bone developed under pathological conditions. For this purpose we examined a small bony nodule developing in the tissues to the inner side of the lower end of the humerus, secondary to trauma and due apparently, as pointed out by Dr. Archibald, to a local separation of portion of the periosteum. In the second place we

examined a portion of a large nodular, pure osteoma of the left frontal bone, obtained from a man twenty years old, which had grown into the cranial cavity and had produced great atrophy of the frontal lobe. [Royal Victoria Hospital—P. M. Reports, No. 15/05.] In neither of these specimens did Sudan III. give any trace of the presence of fat or soap in connection with the more recently growing portions.

THE PROCESS OF DEPOSIT OF CALCAREOUS SALTS UNDER PATHOLOGICAL CONDITIONS.

In the Arterial Wall. We now pass on to tissues which, under pathological conditions, undergo *calcareous degeneration.* Of these first and foremost are the arteries. All specimens examined by us coming from persons over twenty-five years of age showed more or less change in the aortic wall. The change varies from the faint white streaks which are seen through the intima to the condition in which calcareous plaques are present, with and without ulceration.

The most remarkable point that strikes one in staining a series of aortas by the methods here described is the frequent presence of recognizable amounts of calcium salts in the media of adults. (See Figs. 3 and 4.) In the routine examination of eleven specimens of the aorta, from persons varying in age from twenty-two to forty years, which on macroscopical examination showed no lesion other than fatty plaques in the intima, it was found that calcium salts were present in abundance at one time in the media, at others in the intima. It was not infrequently seen that the media was affected by the calcium increase while the intima remained unchanged or was affected by a slight extension only of the process from the media. I hope to call fuller attention to this change in the media in a subsequent article. So far it would seem to have escaped notice.

The white plaques in the intima have long been noted by pathologists and have passed under a host of names. Gross, as early as 1845, spoke of the condition as "atheromatous" and "steatomatous," where he says the microscope "brings into view

a multitude of crystalline plates and fatty granules with albuminous and oily particles." Coplin has collected cases in which the change in the arterial wall was noted as early as the second year of life, but it is not our intention to deal here with the frequency of this affection. What is to be noted is that all vessels with arteriosclerosis have stainable calcium salts in either intima or media to a greater or less extent.

In studying normal aortas taken from young adults we found that neither intima nor media was affected by Sudan III., while only a few fat cells were seen in the adventitia; that is, in a normal and healthy state the intima and media of the aorta show no "microscopical" fat present, and further, when such aortas are stained with silver nitrate solution there is no staining or deposit of silver in the tissues. Obviously the small amount of calcium salts and fat normally present in the tissues is not detected by our staining methods.

Sections were made from the iliac artery of an adult aged thirty years, which was apparently healthy on gross inspection with the exception that here and there white areas of the size of a pinhead and not raised above the surface were present in the wall. The specimen was one which had been picked from a number as a sample of the apparently normal large vessel of adult life. When stained with hematoxylin it was seen that the elastic layer did not follow the lumen of the vessel at an equal distance around the artery, but at the sites of the macroscopical fatty areas the intima was thickened toward and bulged into the media, and here the elastica was distorted and at times broken. Away from these isolated changes in the intima the artery was found to be perfectly healthy. When stained with Sudan III. it was found that these thickenings showed in them the presence of numerous fatty granules, many of which stained an intense reddish yellow. This fatty material lay in aggregated clusters of granular particles of larger and smaller size, situated chiefly at the border zone of the intima next to the media. While these fatty particles were seen in the nodular portion of the intima, the rest of the arterial wall was free.

In the healthy portion of the arterial wall the elastic lamina

did not stain with Sudan III. and followed the lumen of the vessel at an equal distance and in a single strand. As we approached the intimal lesion the elastic layer split longitudinally into a number of strands, which now, instead of retaining a regular wavy contour, became of unequal undulations and spread apparently into the media. The individual strands of the elastic lamina were swollen and fragmented, showing in places a "snapping" of the fibres. In this area of change in the elastica the fibres were also seen to take the Sudan III. stain, which became more intense and more granular as we approached the thickening of the intima. Immediately below the fatty deposits in the thickened intima the elastic fibres were found much split up and composed of short, curly, Sudan III. staining strands.

When we come to examine closely the particles stained by Sudan III. we find them of different characters. First we note the larger droplets or granules, which are not perfectly round, and which are isolated, or else we see several of these fusing into larger masses. The color of these is unmistakably that of neutral fats. Besides these we find many more smaller particles which are distinctly semicrystalline and of a much lighter color, approaching almost to pink. These pink-staining particles we find in greatest abundance along the border zone between the intima and media, and often occupying the elastic lamina itself.

It was found that when consecutive sections were stained alternately with Sudan III. and silver nitrate the silver nitrate was precipitated in areas identical with those picked out by Sudan III., though the relative quantities were unequal, there being proportionately more fat present; that is, the calcium deposit picked out by the silver nitrate occupies the nodular portion of the intima and is not seen in the rest of either intima or media. Further, the portion of the thickened intima picked out is that occupied by the pink-staining granules. In the less affected parts the calcium appears as fine, dust-like material, staining an intense black. Judged by the outline seen as a silhouette against a lighter background the individual granules here are crystalline. In places the elastic lamina was picked out as a wavy line composed of aggregated granules of calcium.

In this specimen we have the early change in the aorta, a condition which we would not yet speak of as arteriosclerosis. The white pinhead patches on the intima are seen to represent areas with fatty substance of two kinds—one an intensely yellowish-red staining material, which is fat, and lighter particles, which from their reaction with Sudan III. can only be soaps; and further, the thickenings in the intima are shown to contain an increase in the calcium content, and this increase to occur in conjunction with the light, soapy, staining material; in other words, the calcium increases side by side with the soap, and the arrangement described suggests strongly that we are dealing here with a deposit of calcium soap.

In another instance there was a generalized thickening of the arteries, though only at the bifurcation of the aorta was any macroscopical calcareous degeneration to be seen. The aorta showed numerous white plaques raised above the surface, and one of these from the abdominal aorta was sectioned. Stained with Sudan III. both media and intima showed numerous aggregations of stained particles. The staining in the intima was confined chiefly to the atheromatous thickening, in which considerable fat-staining masses occurred, while outside the nodule the granules were collected mainly around the elastic lamina. As in the previous case the granules could be divided into two classes—the larger masses, which fused with other contiguous particles, readily recognized as fat deposits, and the smaller, lighter-staining granules, which appeared semicrystalline in shape. In the intima the larger fat masses were in excess of the finer granulations, while in the media the reverse condition existed; that is, the light-staining granules were much in excess of the fat; in fact, only a little fat was to be seen on the boundary between the media and intima. In the rest of the media there were clusters of fine, sand-like particles lying between the elastic layers and forming rows, more or less wedge-shaped, which occupied the position of the muscular fibres. In the media the stained granules were intermingled with numerous unstained refractile bodies, which disappeared from the specimens when treated with acid solutions. On treating the sections with silver nitrate it was

found that the blackened deposit was present in the media in the regions where the Sudan III. demonstrated the light-staining, soapy particles. Similar to the Sudan III. granules, the silver-nitrate deposit was aggregated into clusters lying parallel to and between the elastic fibres. The silver-stained particles in these clusters were much in excess of the refractile bodies seen in the Sudan III. specimens, and they tallied in number with those seen in unstained sections. The distribution of the silver-stained calcium salts was fairly general through the media, the greatest amount being toward the internal surface. (See Fig. 3.)

In the intima, however, there was less calcium to be seen, that present being confined to the atheromatous areas where the deposit seemed to be invading from the media. Beyond the atheromatous plaques there was no lime salt to be seen in the intima excepting a fine, dust-like infiltration along the boundary zone. The whole condition in the arterial wall we look on as consisting of two distinct processes: the change in the media of a chronic nature and of longer standing than the intimal change, the degenerative process with fatty change having been progressive; and the atheromatous condition in the intima of more recent date, owing to which time had not been given for such extensive deposits of calcium salt.

We now undertook to remove all the neutral fats and fatty acids from the sections of the aortas above described by treating them with ether and petroleum ether. They were first washed in 70 per cent. alcohol before subjecting them to the ether. After this treatment the only material remaining which could stain with the Sudan III. would be a soap. On examining the sections stained with Sudan III. (see Fig. 5), it was found that all the bright-red-staining neutral material had been removed and all that remained to take the stain were small crystals of a light salmon-red color. These crystals lie in clusters of fifty or more, the long axis of the clusters being parallel to the direction of the fibres. The clusters are to be found mostly in the intima at the atheromatous area and in this tissue lie some little way inward from the endothelium. In the deeper parts of the intima the clusters become more broken up, and after staining the silver nitrate are seen to

be mingled with calcium deposits, which are absent in the more superficial parts of the intima. Hence, the Sudan III. staining particles which remained near the boundary zone between the media and intima after treatment with petroleum ether are combined with granules of calcium salts, while those apparently of more recent origin lying near the endothelial surface contain no calcium salt. When we examine the aorta beyond the atheromatous patch we lose any evidence of soap in the intima except in the deeper portions near the media, and only as the atheromatous area is approached do the layers between the fibrous strands become widened and the spaces become the site of deposit of soap granules. In the media where, as we have described, the calcium salts are much more marked, similar clusters of granules to those noted in the intima are found, with, however, the difference that in the media the clusters are compounds mainly of silver-nitrate salts—much calcium with a little soap—while in the intima the proportion is exactly reversed.

To resume, it may be stated that by employing suitable methods it is found that calcareous deposits occur in the arterial walls, more particularly in the wall of the aorta, at an earlier age than is usually suspected.

These deposits vary as regards the region first affected. This variation may be in regard (1) to the internal elastic lamina, (2) to the media, more particularly the muscle fibres, and (3) to the intima in areas of nodose sclerosis.

Judging from the treatment of sections for the demonstration of fats and calcareous salts, the stages in this process are (1) degeneration of the affected region with deposit of fatty globules, (2) formation of soaps, mainly with calcium; (3) deposit of calcium salt devoid of a fatty moiety.

The results obtained in connection with calcified deposits in the arterial walls were confirmed and extended by an examination of other conditions of calcareous infiltration.

Calcareous Infiltration of Thickened Pleura. The cases examined were evidently of some duration. There were

thickened fibroid adhesions between the visceral and the parietal pleuræ, and in the centre of the fibroid layers dense calcified plaques occurred. The plaques were found to form rather irregular laminae with somewhat irregular surfaces. By examining the material after decalcification the section through what was a densely decalcified plaque stained a diffuse pale yellow with Sudan III., no individual granules being present; but in the immediate neighborhood of the plaque was an aggregation of masses stained deeply with Sudan III. Therefore, at the periphery where the process of calcification was still continuing there was definite evidence of the presence of fats.

In studying the decalcified sections it was noticed, as frequently observed by others, that the decalcified areas stained more deeply with hematoxylin than does normal tissue. Very few nuclei were recognized. The matrix left behind after removing the calcium salts was of a hyaline nature. The existence of this matrix led Litten and others to the theory that the calcium salts are deposited as calcium albuminates. That the fat or soapy substance, still exist in connection with the matrix is indicated by the light-yellow color given with Sudan III.; and remembering that, as we have noted, soap solutions and albumins form insoluble compounds with which calcium can combine, it would seem more probable that we are again dealing in this instance with the resultant albuminous material deposited after the calcium has separated from the combination to unite with phosphoric and carbonic acids, and possibly to some extent also after a part of the soap has been split off to enter into more soluble combinations.

Calcified Fibromata. A similar condition is found in the calcified fibroma, in which the most extensive infiltration is not in the centre of the fibroid mass but in the outermost layer, whence it is proceeding toward the centre. In each of the specimens examined three zones of change were well marked. In the outermost area (which varied in thickness) when the sections are stained with both Sudan III. and silver-nitrate solution there is seen a dense black mass, the small amount of soap present in this zone being wholly obliterated by the black-stained lime salts.

At the margin of this zone and farther inward clusters of granules are to be seen, some of which stain with Sudan III., others with silver nitrate. At times an individual cluster, black at one end, yellow at the other, can be made out. In this area, between the groups of granules, can still be seen the wavy fibres of connective tissue. This constitutes the second zone. The third zone, farther inward, exhibits granules staining only with Sudan III. Thus there is well-marked fatty change, the presence of calcium soap and finally the presence of calcium salts showing no soapy constituent.

That calcifying fibroid tumors should show a deposit of lime salts at the periphery is a phenomenon of the same nature as has been observed in connection with lithopedia, and with kidneys undergoing calcification after complete cutting off of their blood supply. The fibroid tumor that undergoes calcification is one that is undergoing necrosis through defective blood supply, and the calcareous salts deposited are not those already present in the tissue itself, but those precipitated from the lymph which diffuses into the dead tissue from without. It follows that the diffusible salts are taken up by the first soapy substances with which they come into contact in this process of diffusion, and only when those in the peripheral zone become calcified do the soapy and fatty matters situated more deeply have the opportunity to form calcium compounds.

Calcareous Infiltration of Ovarian and Broad Ligament Cysts. Cysts of this nature, in which a thin shell of lime salts is laid down in the fibrous tissues of the walls, are occasionally encountered. The process is usually confined to a layer bordering on the cyst cavity beneath the lining membrane of the cyst in the surrounding fibrous tissue. In these we have found the usual evidence of fatty change, of soap formation in the immediate neighborhood of the areas and of deposition of lime salts.

Calcareous Tuberculous Nodules. The nodules can be decalcified, cut by the freezing microtome and the sections treated with Sudan III. or Scharlach R. It has been usual of late years to speak of tuberculous caseation as a process of protoplasmic degeneration in which there is very little associated fatty

degeneration. It is interesting therefore to note that by employing the methods described by us it can be demonstrated that the caseous areas which have undergone calcification contain a very considerable amount of fatty matter, so much indeed that the yellow staining areas of the tuberculous nodule stand out very prominently from the surrounding tissue. Treatment of such sections with ether removes some of the material stainable with Sudan III., but by no means all. As might be expected from what has already been said, differences are to be made out between old and more recent calcified tuberculous areas. In dense, old, calcified glands and nodules there is less of the fatty staining material left, and it is only here and there, where the soap moiety has not been wholly removed, that the deposition of the lime salts gives any results with Sudan III., while in softer and less dense nodules larger and smaller granules staining with Sudan III. are abundant. It is noticeable that very little fat is to be made out in the enveloping fibrous tissue. The question naturally arises, Where does this fat come from? Examination of lung tissue in cases of active tuberculosis showed that the fat and its products are already present in tubercles showing the early stages of central necrosis, which as yet scarce show caseation. In caseous tubercles this fatty matter is still more evident, and in these also calcareous salts in the form of fine granules are to be detected. It was only in those tubercles in which the fatty substances were aggregated into larger granules that lime salts could be demonstrated. In the earlier non-caseous areas there was no reaction of the calcium, and it is to be noted that there were more Sudan III. staining granules in the centre of the caseous areas than at the periphery. This series of events indicate the following stages—viz., necrosis, fatty degeneration, formation of calcium soaps and deposition of calcium salts having no soapy moiety.

Pancreatic Fat Necrosis. It has been pointed out by various observers that in pancreatic lesions followed by fat necrosis the neutral fats within the fat cells undergo decomposition, and as a result fatty acid crystals are left behind. These fatty crystals after a time unite with the lime salts of the tissue fluids to form

insoluble calcium soaps. I found that in the experimental production of fat necrosis the fatty acid crystals could be stained readily enough, but unless the animals experimented upon remained alive for more than a week the lime salts were not to be demonstrated microscopically in the lesions; in other words, the combination of the fatty acids with calcium to form calcium soaps is not an immediate but rather a slow process. A definite period of time seems to be necessary before the calcium soaps accumulate so as to be present in stainable quantities. We examined one specimen of hemorrhagic pancreatitis in man and found that fatty acid crystals had been deposited in the peripheral zone of the necrotic area. In this zone calcium salts were seen in small amounts distributed as a fine dust. The specimen, however, was an accidental find in a recent autopsy, two small foci of necrosis in the tail of the pancreas, each scarce one centimetre across, being present, and there was no clinical indication of the length of time that the condition had existed. The earlier observations upon the presence of lime soaps in connection with pancreatic fat necrosis will be referred to later.

The preceding section of this paper may be reviewed as follows:

1. All calcareous infiltrations are preceded by fatty changes, and in them substances are found consisting of neutral fats, fatty acids and soaps which stain with Sudan III.

2. By employing appropriate methods the microscopic fat and fatty acids can be removed, the soaps remaining behind, the last being detected by reason of their differential staining with Sudan III.

3. The granules in certain regions which give the soap reaction with Sudan III. give also the calcium reaction with silver nitrate.

4. As the process of calcification advances many of the masses deposited in the part no longer stain with Sudan III., but only react for calcium salts.

In areas undergoing calcification three zones are to be made out: (1) The oldest zone of complete calcification, exhibiting dense calcareous deposit lying in a hyaline matrix. In this zone

little soap or fatty substance is to be demonstrated. (2) The intermediate zone, in which granules of lime salts and soap granules are in close apposition; some of these granules give both the calcium and the soap reaction. (3) The most recent zone, which gives the reaction for fat, fatty acids and soaps and fails to reveal calcium salts in sufficient quantities to be recognized under the microscope.

ON THE PRESENCE OF SOAPS IN THE ORGANISM UNDER PHYSIOLOGICAL CONDITIONS.

Since the observations above detailed indicate that soaps play a most important part in the process of pathological calcareous change, it appears desirable to compare them with observations made upon the part played by the soaps in the physiology of the animal economy.

In 1857 Marcet stated that during fat digestion the fats are converted into soaps in the intestinal canal, and these soaps are absorbed by the intestinal mucosa. The absence of any amount of soaps in the blood comparable with the amount of fat absorbed led others to conclude that the soaps as such did not pass beyond the endothelial cells, and to suppose that a glycerin molecule is furnished by these cells, the reconstructed fat being passed into the lacteals. Heidenhain pointed out that some at least of the fats are taken up by the leucocytes on the surface of the intestine and are carried by them directly into the lacteals and blood-vessels. More recently Ramond has denied the validity of Heidenhain's observations, and has concluded that the greatest part of the fat absorbed enters the portal system and not the lacteals, and enters in the form of soap and not of fat. From this statement I infer that Ramond regards the soap as becoming transformed into fat during its passage from the endothelial cells to the portal capillaries. He finds also that the liver tissue contains a ferment capable of splitting fats into their respective fatty acids. Beneke and later Hoppe-Seyler have pointed out that the blood normally contains soap in solution. Beneke makes an interesting suggestion of the manner of recovery from

pulmonary fat embolism. He points out that possibly a solution of the fat of the emboli is brought about through the action of the lipase present in the blood, which converts the fat into a soluble soap. He also states that fat inoculated subcutaneously disappears so rapidly that the only satisfactory explanation is one based on its conversion into soluble soap.

Still more recently Schultz, who studied fats as a whole in the blood, found that no less than 28 per cent. of the total fatty acid obtainable is present in combination as soap. During starvation, when the fat deposits are used up, he found an increase of the fat in the blood and concluded that the fat is transported from its normal deposits by way of the blood. The fat in the tissue cells, he holds, becomes transferred into soap, and thus passes in solution into the blood.

As to the manner of conversion of the fats into the fatty acid, in which form combination occurs with alkalies to produce soaps, we have the observations of Hanriot. This observer found that blood serum, pancreatic juice and liver juice contain a ferment capable of converting the neutral fats into their respective fatty acids. This ferment was not present in muscle tissue, testicle or thyroid gland. The substance isolated by Hanriot seemed by its action to be a true ferment, and was present in all the animals examined. He made a distinction between pancreatic lipase and serum lipase, claiming that they are different substances chemically. Cohnstein and Michaels, who also found a lipolytic ferment in the blood, differ from the former observer in believing that it is present in the red blood cells rather than in the serum.

There can be little doubt that the leucocytes and endothelial cells play parts in the synthesis of fat. It is well known that leucocytes are fat-carriers and that they transport fat from the intestinal canal during fat digestion. The quantity of fat transported must be very small indeed, but Arnold has found that subcutaneous injection of soap solutions into the backs of frogs attracts leucocytes which become filled with fat, and he also noted that eosinophilic leucocytes are especially active in this fat synthesis. Fischler has shown by similar experiments that sub-

cutaneous injections of soap are followed by deposit of fat in the organs, and that when a soap solution is passed through the renal vessels the fat particles can be seen between the endothelial cells and in the kidney tissue. Hence it would seem that endothelial cells take part in the conversion of soap into fat. This view is also supported by the statements of Ramond, namely, that the fat from the intestine passes through the intestinal mucosa, as through a dialyzing membrane, in the form of soap and is reconstructed on entering the portal system.

Munk studied the toxicity of soap and pointed out that soap solutions injected into the portal vascular system are only one-sixth as toxic as when inoculated into the peripheral vessels. From this it would seem that the portal endothelium or the liver parenchyma are especially active in converting the soaps into neutral fats.

THE PRESENCE OF SOAPS IN THE ORGANISM UNDER PATHOLOGICAL CONDITIONS.

It is not a little remarkable that very few observations upon the part played by soaps in pathological conditions have appeared in the literature. We have encountered isolated notes only upon the subject, and do not know a single research, properly so-called, in which their role has been fully worked out. Many years ago Virchow called attention to the presence of calcium salts in degenerating lipomata, and very correctly concluded that the fats present in these tumors combine with the calcium salts to form soaps. Kyber in 1880 referred incidentally to the part which alkalies and fatty acids must play in the process of calcification. Somewhat later Jaeckle and others enunciated the theory that the formation of soaps is one step in the process of calcification of fatty tumors. But this theory has to our knowledge never been tested experimentally and would seem to have become obsolete. In 1890 Langerhans pointed out that in fat necrosis following pancreatic lesions crystals of fatty acids appear and in many cases unite with calcium of the blood to form an insoluble calcium stearate which occurs at the site of the lesion. It does

not appear that Langerhans ever continued these observations or expanded his findings so to apply them to calcification in general.

Quite recently Fischler has published a preliminary note upon certain methods for detecting the presence of fats and soaps in the tissues; and though he does not state it definitely, he nevertheless seems to imply that his observations point to an important part played by soaps in more than one process.[1]

As indicated in the preceding pages, our observations all point to the fact that the formation of soaps is a necessary step in the development of pathological calcification. I may at this point bring together our further studies on the chemistry of this process.

The analysis of aortas which were in the process of calcification yielded calcium soaps in small quantities together with sodium and potassium soaps, though chemical extraction did not give as clear an idea of the process as was obtained by treating sections with petroleum ether and later with Sudan III. Sections so treated seemed to indicate the presence of a fair amount of soaps. By analysis the quantities obtained were very small. Indeed, the Sudan III. stain after treatment seemed to show clearly that substances which *in vitro* are soluble are relatively insoluble when present in the tissues. For instance, sodium and potassium soaps are, as we know from every-day experience, easily soluble substances, while, on the contrary, calcium soaps are relatively insoluble. We were prepared, therefore, to find that the tissues contain relatively small amounts of the former large amounts of the latter, supposing that when formed locally sodium and potassium soaps would diffuse into the blood and lymph and so escape to a very large extent; but to our surprise the sodium and potassium soaps were not nearly so soluble in tissues as they are *in vitro*—in fact, they are relatively insoluble in the former location.

[1] The number of the *Centralblatt* containing Fischler's article reached America, I may add, after I had forwarded to Philadelphia the abstract of my preliminary communication upon this subject, which was read at the meeting of the Association of American Physiologists in December, 1904. A study of Fischler's paper will show that he has reached his conclusions by the employment of methods differing from those given here.

ON THE EXISTENCE OF A COMPOUND OF SOAPS WITH ALBUMIN.

What would seem clearly to be the explanation of this difference was discovered in conducting observations in the test tube. Doubtless the reaction which we are about to describe has been noted before, but, if so, it has failed to come to our attention. If to a weak solution of a pure soap—sodium stearate for example, though the same is true of the oleate and the palmitate—there be added dilute egg-albumin, a white rather flocculent precipitate forms. The reaction is not immediate: at the temperature of the room it requires half an hour or longer before it is complete; the precipitate is a combination of soap and albumin. The compound is slightly soluble in water and less soluble in alcohol. Under the microscope the precipitate appears granular, and when the particles are treated with Sudan III. they assume the identical pinkish-yellow color of the soap granules observed in tissues undergoing calcification.[1]

It is worth noting that the precipitate becomes denser and more pronounced when carbon dioxide is passed through the solution. Acid calcium phosphate may be added to a solution of egg-albumin without precipitation; but if the salt be added to a combination of weak soap solution and egg-albumin, made as above, precipitation takes place rapidly and yields a dense sediment.

The Chemical Isolation of Soaps from Pus. We have already stated that we have been able to isolate soaps from more than one order of calcified tissue. We were able to isolate a material soluble in absolute alcohol, insoluble in petroleum ether and precipitable on the addition of acid calcium phosphate from a number of calcified tuberculous glands of the mesentery. On the addition of a mineral acid the fatty acid was isolated from this combination and gave the characteristic stain with Sudan III.

[1] Mr. O. R. Mabie, Phm.B., has undertaken a study of this soap-albumin compound. His studies are at the present incomplete, but he has found that solutions of albumin when mixed with known strengths of chemically pure soap solutions absorb a certain quantity of the soap. He has used albumin from different sources, and with all he has obtained similar results, although different degrees of absorption have resulted.

Particular attention is called to the fact that similar soaps may be present in pus. The cases from which the pus was examined were, it is true, of chronic nature; and no opportunity has yet come to us for the study of large quantities of pus of more acute origin. With the pus of two tuberculous abscesses (one an empyema, the other a case of Pott's disease), each yielding fifty cubic centimetres, tests were made. Each quantity was extracted with warm absolute alcohol for seventy-two hours, after which the mixture was filtered and the filtrate evaporated to complete dryness. The residue consisted of fat drops mixed with a white granular substance. The residue was collected and washed with ether and petroleum ether for four days, after which no fat or fatty acid could be demonstrated in the filtrate. It was now digested with warm distilled water, and on the addition of calcium chloride to a quantity of the watery extract a white precipitate, stainable after evaporation on a watch glass with Sudan III., was obtained. In the unstained condition the precipitate appeared as a white fine powder. Fatty acids were obtained from the residue by adding acids, and the addition of hydrochloric acid to the aqueous solution caused an opalescence in the test tube. Sodium and potassium were detected in the residue by the flame, but no calcium was found. Fatty acids could also be detected and saponified from the extract in the petroleum ether.

THE EXPERIMENTAL PRODUCTION OF CALCIFICATION.

In Capsules Containing Fats and Fatty Acids. Early in the course of this research experiments were undertaken to determine the organic compounds with which calcium salts may unite. Various products obtained as pure soaps were placed in celloidin capsules prepared by the method recommended by McCrae and introduced into the peritoneal cavity of rabbits, where they were left for several days. The results of these experiments led to the study of the role of fatty acids and soaps in the process of calcification.

Von Kossa places the normal calcium strength of the blood of rabbits as varying from 1.06 to 2.01 per cent., which may be

taken as about the limits of range. In our experiments two celloidin capsules were prepared containing one gram of sodium stearate and one gram of sodium palmitate respectively. These were inserted into the peritoneal cavity of a rabbit and allowed to remain there eleven days. On removal the contents of the capsule were more or less caked and contained some serum. The contents were treated with hydrochloric acid and precipitated with ammonium oxalate, and the solution then rendered alkaline with ammonia. The precipitate was collected and the calcium determined in the ash obtained on ignition. The sodium stearate was found to have combined with the greater quantity of calcium, there being 4 per cent. of the alkaline earth present. The capsule containing the sodium palmitate was found to contain 3.8 per cent. of calcium. Hence, it was found that even in the short space of eleven days a definite conversion of the sodium and potassium soaps to those containing calcium had taken place. Other experiments were carried out in which fatty acids, stearic and palmitic were substituted for their salts. The results were similar to the first, there being a decided increase in the calcium strength over that present in the serum of the animal.

Experimental Calcification in the Kidney. All cells use fat in some form in carrying out their normal physiological function, and, as has already been pointed out, a great deal of fat is brought to them as soap. When the cell is injured the soap, it would seem, is not metamorphosed but remains fixed in the cell in combination with the cytoplasm. This form of union is indicated by experiments on the kidney epithelium in animals, for the main conclusions to be drawn from Litten's experiments are that the tissue cells undergoing calcification are in a degenerating state, and have already lost or are in process of losing their vitality. He further pointed out that calcification proceeds more rapidly if along with the dead and dying cells there should remain a good circulation to supply the calcium and other materials which are eventually deposited as a permanent precipitate. As Litten examined his sections only with hematoxylin staining he found no evidence of fatty products laid down in the areas of his "coagulation necrosis."

The animal experiments reported by Litten were the first dealing with the question of the calcification of the renal tubules. They demonstrated that if the renal vessels were ligated for two or more hours and then loosened after eight or ten days crystals of lime salts were to be found in the cells of the convoluted tubules chiefly. The better the blood supply to the organ after ligation, the more quickly did the calcification proceed. The explanation offered was as follows: Arrest of the blood to the kidney having caused "coagulation necrosis" of the tubular epithelium, the latter advent of the calcium-containing tissue fluids brought about precipitation in the tubules of "calcium albuminate." Although this theory of Litten has been current for twenty years, it is noteworthy that the production of calcium albuminate had not been demonstrated *in vitro*.

We must, however, conclude that in the cells which are injured there is a change in the protoplasm, and of this there is adequate evidence found in the fact that the nuclei stain poorly and the cell substance appears swollen and homogeneous. The alteration of the nucleus is perhaps the chief indication that the cell has suffered grave metabolic changes. There is no evidence at this point of the process that the cell substance is diminished in amount; indeed, on the contrary, the actual amount of cell material appears increased. This is in keeping with the recent observations which point to the conclusion that fat appearing in the cell is not the product of cytoplasmic decomposition, but is absorbed from without. The view I wish to emphasize is that in the degenerating cells absorption of material from without still continues, whether this material be albuminous or fatty. But owing to nuclear disturbance, or more broadly to lowered metabolic activity, the substances so absorbed cannot be used up. They no longer become combined into the cell cytoplasm or bioplasm proper, and remaining in an uncombined state, may now become subject to various pathological changes.

Neuberger has shown that a number of chemical irritants produce the same effect on the kidney as ligating the renal vessels, and that they lead to calcification of the same sets of tubules. We repeated Neuberger's experiments, using the salts of the

heavier metals—mercury, copper, lead, etc.—with the result of producing calcareous degeneration in the convoluted tubules of the cortex of the kidney. The rabbits were inoculated subcutaneously with solutions of the soluble salts of these metals and then killed after ten days. A small portion of the kidney was removed for microscopical purposes. Frozen sections were stained with Sudan III. and silver nitrate and both gave satisfactory pictures. In consecutive sections it could be shown that the degenerated tubules which reacted for the fatty substances with Sudan III. also reacted with silver nitrate; and, moreover, that when a section was treated first with Sudan III. and after staining was subjected to silver-nitrate solution all the Sudan III. staining tubules were covered over by the intense black stain of the silver salt; that is, the identical tubules which were shown to contain a fatty staining substance also contained calcium salt. (See Figs. 1 and 2.) The calcium could be wholly removed from the tissue by the use of dilute acids without affecting its fatty staining qualities. If frozen sections were treated first with 70 per cent. alcohol and later with petroleum ether, it was still possible to find the tubules picked out with Sudan III. and silver nitrate. Finally, it has been possible to extract from the cortex of the kidney potassium, sodium and calcium soaps. These results indicate that the formation of a calcium soap is one stage in the process of calcification in the kidney; that degeneration and death of the cells being effected the cells are not able to utilize the potassium and sodium soap brought by the blood, and hence they are precipitated in combination with albumins, and later the calcium from the tissue fluid and blood is fixed in an insoluble state by this compound. While we agree with Litten, Neuberger, von Kossa and others that necrobiosis, improperly referred to by them as a "coagulation necrosis," occurs, we look upon this as only one stage in the whole process of calcification.

Von Werra believes that such degenerated cells of the kidney may return to a normal condition. We can hardly accept this view, as calcareous degeneration of cells is the last stage in a pathological process in which the cells and nuclei are disinte-

grated. Hence, it is improbable that they can regain their vitality.

Tartarini-Galleani claims to have studied the kidneys of rabbits after injecting bichloride of mercury into the substance of the organ. He states that the lesion produced is a tissue destruction followed by fibrinous coagulation, which after the ninth day becomes impregnated with calcium salts. The calcification of the kidney remains circumscribed to the area of the organ directly affected by the injection, and he holds that it is neither preceded nor accompanied by the phenomenon of fatty change. I have repeated his experiments in two rabbits and in each the result was different from that described by him.

Sections of the inoculated kidney treated with Sudan III. showed the cells of the convoluted tubules to be swollen and filled with fatty granules. The tubules were well outlined from the surrounding tissue by reason of the stained fat in the cell contents. The glomeruli and the interstitial tissue appeared unchanged, while the arterioles of the cortex showed Sudan III. stained granules in their walls. These granules were distributed more loosely than was seen in the epithelium. The affected convoluted tubules presented collections of irregular granules staining not so intensely as neutral fat but rather a brownish yellow. The tubules in the pyramids showed a striking difference. While they were less affected than in the cortex, the condition of the fat in them differed from that of the convoluted tubules. The individual cells showed no change in size or shape and the nuclei retained their staining power. However, the Sudan III. picked out numerous fine globules situated toward the inner margins of the cells—that is, toward the lumen and away from the nucleus. In some cases it appeared that the fatty globules were in the process of being extruded into the lumen. The Sudan III. granulation noted in the straight tubules was of the character of neutral fat. No calcium deposit could be demonstrated in the straight collecting tubules, while in the cortex the convoluted tubules, which showed the Sudan III. granulations, reacted to silver nitrate in the manner of calcium salts.

Resume. Our studies upon experimental calcification in the kidney confirm and extend the observations made upon calcareous changes in human tissues. If the tubules become the seat of the calcareous deposit it is possible to recognize the following stages, viz.:

1. A stage of cell degeneration characterized by swelling of the cell substance and diminution of the nuclear chromatin, the cells becoming swollen and homogeneous.

2. A later stage in which fat appears in the cells, apparently having arisen by absorption.

3. A final stage in which calcareous salts appear in the cells accompanied by soaps. An intimate relation between cytoplasmic degeneration and the formation of insoluble soaps would seem to exist. Judging from observations made in test tubes the relatively insoluble soaps are compounds between soap and certain albuminous matters liberated from the cytoplasm. The calcium from the tissue fluids and the blood becomes fixed by the albuminous soap compound.

Experimental Calcification of Muscle Fibres. That muscle fibres may become the seat of calcareous deposits is well known. We inoculated a weak solution of bichloride of mercury into the quadriceps muscle of a rabbit, killing the animal at the end of eight days. On examination the muscle at the site of the inoculation showed extensive degeneration and softening. Individual fibres were swollen, and in some places the sarcolemma was broken. Other swollen fibres showed band-like constriction; still other muscle fibres were completely broken down and invaded by numerous polymorphonuclear leucocytes.

The degenerated muscle fibres proved an interesting study. A fine granulation not found in healthy fibres and staining in Sudan III. occurred in their substance, besides which leucocytes loaded with fat globules invaded the degenerating fibres and lay in the interstitial tissue. The fatty staining material within the leucocytes appeared in the form of large and small granules, but these did not coalesce to form large fat globules, as is seen in adipose tissue.

The question arises as to whether the leucocytes are bringing the fat to the injured tissue or taking it away. I am inclined to the latter view, for among the degenerated fibres were some in which the sarcolemma was intact and which were free from leucocytic infiltration, but which nevertheless contained granules staining with Sudan III.; moreover, the leucocytes at the margin of the injured tissue contained no fatty staining material.

We think it probable that this process is not unlike that described in the kidney—namely, a state of lowered vitality of the individual cells through which they, being no longer able to deal with the fatty material brought to them in solution, form with it a relatively insoluble compound in the cytoplasm of the degenerating cells.

Experimental Fat Necrosis. In order to investigate further the changes which fatty products undergo in the body, we produced fat necrosis in a rabbit by the intraperitoneal inoculation of fresh extract of pancreas. The injection was repeated on the second day and the animal killed on the fifth day. At the post-mortem a few tags of fat necroses, about the size of a pea, were found scattered in the mesentery and the posterior abdominal wall. Frozen sections of these showed that the fat did not exist in the large distended fat cells, but that the globules were replaced by numerous fine crystalline particles staining with Sudan III. On treating the sections with silver nitrate the subperitoneal margins of the fat necrosis showed the presence of a slight amount of calcium salts, appearing like a fine, dust-like deposit. All the areas of fat necrosis did not show the presence of calcium with silver nitrate.

As already stated, Langerhans showed in 1890 that calcium salts appear in the areas of fat necrosis. He describes the process as one in which the fat is converted by ferment action into fatty acid. The calcium salts of the blood then become attracted to the fatty acid moiety and form a calcium soap.

On the source of the fat in the degenerated cells.

Before concluding it is, we think, essential to indicate our views regarding the source of the fat present thus in all cells that

undergo calcification and essential for the due development of the process. To discuss the matter adequately would demand that the numerous recent studies upon fatty degeneration be passed in review: such full discussion would carry us too far afield. It must suffice that we call to mind the reasonable deductions from the work of recent observers which appear to bear immediately upon our present problem.

We may, I think, in the first place safely accept that fats are absorbed by the cell from the surrounding medium in the form of diffusible soaps. Taken up by the cell these soaps may either be reconverted into neutral fats and stored as such in the cytoplasm or may undergo assimilation proper, becoming part and parcel of the cell substance. That such assimilation does occur with associated loss of individuality on the part of the fats is, we hold, demonstrated by sundry recent observations. Thus Rosenfeld and others have shown that kidneys presenting no fat recognizable by microchemical means will, nevertheless, yield upon careful analysis as much as 15 per cent. of fats; and Doremeyer, that mere extraction by ether will not liberate the greater part of tissue fats: the cells have to be digested with pepsin before all can be isolated, a clear indication that the fats have previously been in combination with proteid substances in the cells.

If, then, these possibilities be accepted, it follows that the appearance of fats and soaps in a degenerating cell may be from at least two sources, namely:

1. The absorption of soaps from the circulating lymph and blood, the cell still retaining the power of splitting off the fat, but being unable to utilize this in metabolism, so that it becomes stored up in a non-diffusible form.

2. Disintegration of the cell substances, so that the fats become liberated from their combination with the cytoplasm and appear in the form of discrete particles or globules of neutral fat, which now reveal their presence by reacting with Sudan III.

A third possibility has to be kept in mind, namely, that soaps may be absorbed from the blood and lymph by cells with vitality so depressed that no conversion takes place of the absorbed

soap into neutral fat, but combining with the disintegrated albuminous molecules this forms a relatively insoluble soap-albumin compound.

Into the controversy regarding the formation of fat by the decomposition of the albuminous molecule I will not enter save by suggesting that the opposing views may possibly be harmonized through the demonstration here afforded that albumins form a combination with soaps. The increase in fats determined in tissue autolysis by Waldvogel, Hildesheim and Leathes, Landsteiner and Mucha and others is, it may be, to be explained not as due to the appearance of a decomposition product of the albumin molecule proper, but as brought about by dissociation of this albumin-soap compound.

The time is not ripe for, neither do our personal observations up to the present permit, any discussion of the part played by cell ferments in any of these processes.

As to which of the above alternatives, absorption or dissociation is the more frequently in action as a precursor of calcification, we would point out that when the cell becomes distended with fatty globules (and this is common in atheromatous areas) we must conclude that absorption from without is, in the main, responsible for the condition.

Description of Plate.

Fig. 1. Kidney from rabbit which died eight days after inoculation with corrosive sublimate. Frozen section stained with Sudan III. showing the fatty condition of certain convoluted tubules.

Fig. 2. Section from the same kidney as Fig. 1, stained with silver nitrate followed by weak safranin. Similar convoluted tubules picked out by the silver deposit as seen in Fig. 1 with Sudan III.

Fig. 3. Aorta with large fat masses toward the lumen with similar lighter staining particles near the boundary zone between the intima and media. In the media the blackened deposit representing calcium salts is very intense and is arranged in parallel rows. These rows with higher magnification are seen to be composed of numerous small crystals. Among these rows of calcium salts are also seen the yellowish granules of Sudan III. staining.

Fig. 4. Section of aorta stained with Sudan III. The fatty plaque shows a lighter stained part in its middle, representing the area of soap formation and calcium deposit.

Fig. 5. Same aortic plaque as seen in Fig. 4, treated with silver nitrate solution. The area which with Sudan III. stained a light yellow is now represented as the black deposit the site of the calcium salts.

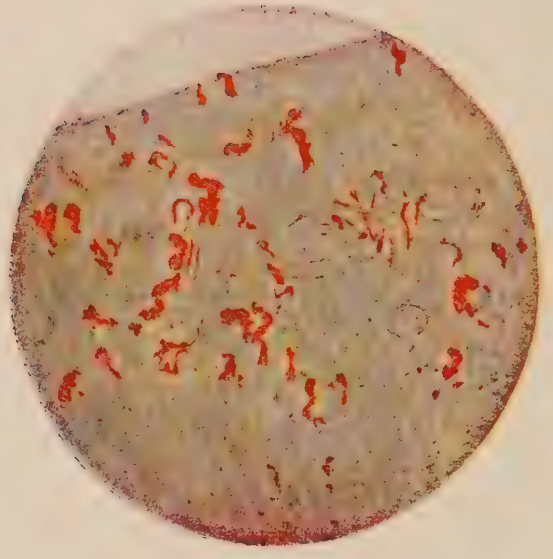


FIG. 1.

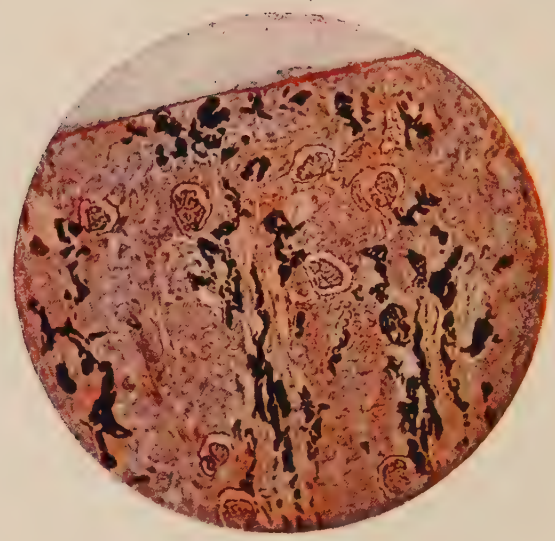


FIG. 2.

FIG. 3.

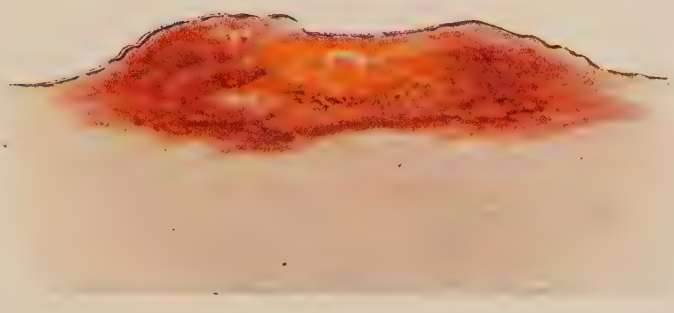


FIG. 4.

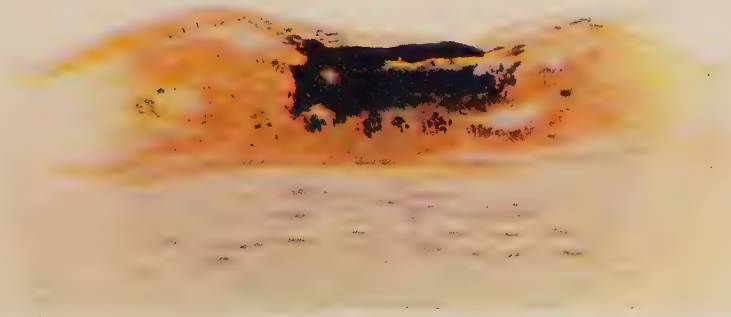


FIG. 5

CONCLUSIONS.

It will be seen from the above that we have studied the conditions associated with the deposit of calcareous salts: (1) In connection with normal and pathological ossification, and (2) in pathological calcification as exhibited in (*a*) atheroma of the vessels; (*b*) calcification of caseating tuberculous lesions; (*c*) calcification of inflammatory new-growth, and (*d*) degenerating tumors; and we have induced experimentally deposits of calcareous salts in the lower animals: (*a*) within celloidin capsules containing fats and soaps; (*b*) in the kidney, and (*c*) in connection with fat necrosis.

I. We have found that bone formation and pathological calcareous infiltration are wholly distinct processes. In the former there is no evidence of associated fatty change, and the cells associated with the process of deposition of calcium are functionally active. In the latter there is an antecedent fatty change in the affected areas, and the cells involved present constant evidences of degeneration. The view that would seem to account best for the changes observed in the latter case is that with lowered vitality the cells are unable to utilize the products brought to them by the blood, or which they continue to absorb, so that the normal series of decompositions associated with their metabolism fails to take place, and hence they interact among themselves in the cytoplasm, with the result that insoluble compounds replace soluble ones.

II. Besides the fact that calcification is always preceded by fatty change within the cells another fact should be emphasized, namely, that combination of the fats present with calcium salts to form calcium soaps tends to occur. The stages immediately preceding these are difficult to follow with anything approaching certainty, perhaps because the earlier stages vary under different conditions. In fat necrosis, for instance, the cells affected are normally storehouses for neutral fats, and as long as they remain healthy neutral fats alone are present in them. When they are subjected to the action of the pancreatic juice with its fat-splitting ferment the cells are killed, and coincidently the neutral fats are decomposed, fatty acids being deposited. The fatty acids

now slowly combine with the calcium salts. In degenerating lipomata the process would seem to be similar.

But in other cases the cells are not obviously fat-containing in the normal state; nevertheless, prior to calcification they undergo so-called fatty degeneration, which is really a form of cell degeneration accompanied by fat infiltration. As regards the source of the cell fats in general we may safely accept:

1. That fats are transported in the blood as diffusible soaps.

2. That taken up by the cells these soaps may either (*a*) be reconverted into neutral fats and become stored in the cytoplasm as such, or (*b*) undergo assimilation proper, becoming part and parcel of the cell substance, in which case they are not recognizable by the ordinary microchemical tests.

3. If these two possibilities be accepted it follows that the appearance of fats and soaps in the degenerating cell may be due to either (*a*) absorption or infiltration of soaps from the surrounding medium, the degenerating cell retaining the power of splitting off the fat, but being unable to utilize this in metabolism; (*b*) cytoplasmic disintegration with dissociation of the soap-albumin combination, or, more broadly, liberation of the fats from their combination with the cytoplasm.

The appearances seen in the cells of atheromatous areas indicate that the first of these does occur.

III. In areas undergoing calcareous infiltration we have demonstrated the presence of soaps, and this often in such quantities that they can be isolated and estimated by gross chemical methods. By microchemical methods also we have been able to show that after removing all the neutral fats and fatty acids by petroleum ether there remains behind a substance giving with Sudan III. the reaction we associate with the presence of soap; and experimentally we have produced these soaps within the organism, more particularly by placing capsules containing fats and fatty acids within the tissues, and after several days finding that the capsules contain calcium soaps and possess a calcium content far in excess of that of the normal blood and lymph.

IV. While these are the facts, certain of the details of this reaction demand elucidation. The existence of sodium and it may

be potassium soaps in the degenerated cells is comprehensible if we accept that these are present in the circulating lymph and simply undergoing absorption; but even then, as these are diffusible substances, how is it to be explained that they become stored up in these particular areas?

We have found that as a matter of fact in regions which give the reaction for soaps, but which give no reaction for calcium (which therefore presumably contain at most amounts of the insoluble calcium soaps too small to need consideration), the ordinary solvents for potassium and sodium soaps do not forthwith remove the stainable material; they are relatively insoluble.

The reason for this insolubility is suggested by the observations made in the test tube, that soap solutions mixed with solutions of white of egg or blood serum form a precipitate of combined soap and albumin, which likewise is insoluble in water and alcohol. The indications are therefore that in cells undergoing degeneration, with degeneration of the cytoplasm, certain albuminous molecules unite with the soaps present to form relatively insoluble soap-albuminate.

V. With regard to calcium soaps, these are also present and in certain stages appear to be the dominating form in the affected tissues. Two questions suggest themselves—viz., what is the source of the calcium and what is the process by which these soaps become formed?

As to the source, the amount present in well-marked calcification is far in excess of the normal calcium contents of the affected tissue. If in the kidneys of experimental calcification three hundred times as much calcium may be present as in the normal kidney (von Kossa), the calcium must be conveyed to the part by the blood and lymph, and that this is so is demonstrated, as we have pointed out, by the distribution of the infiltration in solid organs that, like ovarian fibroids, have undergone necrosis, in which the earliest deposits are superficial.

As to the process there are three possibilities:

1. That sodium and potassium soaps and soap albuminates are first formed, and that interaction occurs between them and

the diffused calcium salts from the lymph, the less soluble calcium replacing the sodium and potassium.

2. That under certain conditions the calcium salts act directly on the neutral fats present in the degenerating cells.

3. That the neutral fats are first broken down into fatty acids and that these react with the calcium salts to form the soaps.

We are assured that the first process occurs, and that because in the boundary zone of areas of calcification we can detect soapy particles devoid of calcium, identical in position and arrangement with the particles more deeply placed which give the calcium reactions. But this is not the only reaction. In case of fat necrosis we see clearly that the third process is in evidence. And we are far from being convinced that the second does not also obtain. We have been impressed by the large accumulation of neutral fats in the cells in cases of early atheroma and the absence of any stage of the process of recognizable fatty acid. While soaps, it is true, are compounds of fatty acids with alkalies, it is recognized in ordinary domestic life that they can be formed by the direct action of strong lye upon ordinary fats, and this even in the cold. It is quite possible, therefore, that there occurs a similar direct process in the organism.

The point is worth noting, however, that this does not occur in healthy cells, the seat of fatty infiltration. We therefore leave this an open question, only laying down that, as indicated by the hyaline albuminous matrix left when calcium salts are dissolved out of an area of calcification, there must exist a calcium soap or fat albuminate similar to the potassium and sodium soap albuminates already mentioned—such an albuminate as we can form with calcium soaps in the test tube.

VI. In old areas of calcification soaps are largely if not entirely wanting, although these are to be detected at the periphery, when the process is still advancing. The reactions given by these older areas are almost entirely those of calcium phosphate, though some calcium carbonate is at times to be made out.

This seems surely to indicate that the final stage in calcification is an interaction between the calcium-soap albuminates and substances containing phosphoric and carbonic acids. Such sub-

stances, it is needless to say, are present in considerable amounts in the lymph and blood. We must conclude that the acid sodium phosphates of the lymph act on the calcium soap, the highly insoluble calcium phosphates being formed (? plus the albuminous moiety of the original compound) and diffusible sodium soap being liberated, while similarly alkaline carbonates form calcium carbonate and liberate sodium and potassium soaps. Calcium phosphate and calcium carbonate thus become the insoluble earthy salts of old crystalline areas of calcification.

VII. As already stated very little soap is to be found in these old areas. It is possibly worth suggestion that the soaps liberated in this last reaction, as they diffuse out, again react with diffusible calcium salts and form calcium soaps which once more react with the alkaline salts to produce the phosphates and carbonates; that, in short, they have a catalytic action. Certain it is that old calcareous areas are extraordinarily dense, and have a coarse crystalline structure, wholly at variance with the finely granular appearance of the more recent areas, and these large crystalline masses, it would seem, can only be formed by successive deposition of new material and eventual fusion, as the interspaces become filled in between the original masses.

In conclusion, I wish to thank Professor R. F. Ruttan, of McGill University, and Mr. J. R. Roebuck, B.A., for their kind assistance in carrying out some of the chemical analyses, and Drs. M. E. Abbott and F. A. J. Lockhart for specimens of calcareous degeneration of tumors.

Bibliography.

Arnold. Münchener med. Wochenschrift, 1902, xlix. 1945; Virchow's Archiv, 1903, clxxi. 197.

Beebe. American Journ. of Physiology, 1904, xii. 167.

Beebe and Buxton. American Journ. of Physiology, 1904, xii, 466.

Beneke. Ziegler's Beiträge, 1897, xxii. 343; Virchow's Archiv, 1900, clxi. 194.

Cohnstein and Michaels. Pflüger's Archiv, 1897, lxv, 473.

Dormeyer. Pflüger's Archiv, 1897, lxv. 90.

Fischler. Virchow's Archiv, 1902, clxx. 100; Virchow's Archiv, 1903, clxxiv. 338; Centralblatt f. Pathologie, 1904, xv. 913.

Gierke. Inaugural Dissertation, Berlin, 1902.

Hanriot. Archiv de Physiologie, 1898, x. 797.

Hildeshein and Leathes. Jour. of Physiology (Proceed. of Physiolog. Soc.), 1904, xxxi. 1.

Irvine and Sims Woodhead. Laboratory Report, Royal College Physicians, Edinburgh, 1889, i.; 1890, ii.

Jaeckle. Hoppe-Seyler's Zeit. f. Physiol. Chemie, 1902, xxxvi. 53.
v. Kossa. Ziegler's Beiträge, 1901, xxix. 163.
Kraus. Verhandlungen d. deutsche path. Gesellschaft, 1904, 37.
Kyber. Virchow's Archiv, 1880, lxxxi. 436.
Landsteiner and Mucha. Centralblatt f. Path , 1904, xv. 752.
Langerhans. Virchow's Archiv, 1890, cxxii. 252.
Litten. Zeitschr. f. klin. Med., 1879, i. 131; Virchow's Archiv, 1881, lxxxvi. 508.
McCrae. Jour. of Experimental Medicine, 1901, v. 635.
Marcet. Proceedings of Royal Society, 1858, ix. 306.
Munk. Cent. f. d. med. Wissensch., 1889, 514.
Neuberger. Archiv f. exp. Path. u. Pharmacol., 1890, xxvii. 39.
Pfahler. New York Medical Journal, 1902, i. 270.
Ramond. Ref. bulletin d. l'inst. Pasteur, 1904, ii. 726; Archiv. d. méd. exp. et. anat. path., 1904, xvi. 655.
Ribbert. Verhandlungen d. deutsche path. Gesellschaft, 1904, 48.
Rosenfeld. Verhandlungen d. deutsche path. Gesellschaft, 1904, 73; Berlin. klin. Wochenschrift, 1904, xli. 34.
Schultz. Pflüger's Archiv, 1897, lxv. 299.
Schultz and Schwalbach. Pflüger's Archiv, 1894, lv. 231.
Schwalbe. Verhandlungen d. deutsche path. Gesellschaft, 1904, 71.
Tartarini-Galleani. Lo Sperimentale, 1904, viii. fasc. 3; Ref. Medical Chronicle, 1904, xli. 116, and Centralblatt f. allg. Path., 1905, xvi. 687.
Traina. Ziegler's Beiträge, 1904, xxxv. 1.
Virchow. Virchow's Archiv, 1856, ix. 618; 1859, 103.
Waldvogel. Virchow's Archiv, 1904, clxxvii. 1.
v. Werra. Virchow's Archiv, 1882, lxxxviii. 197.

EXPERIMENTAL ARTERIOSCLEROSIS.*

By RICHARD M. PEARCE, M.D., and E. MacD. STANTON, M.D.

(From the Bender Laboratory, Albany, N. Y.)

The complexity of the pathologic picture in the arteriosclerosis of man and the difficulty of determining the nature and sequence of the early changes have led many investigators to attempt the experimental production of the disease in the hope of thus solving some of its many confusing problems. Until within the last two years all such efforts have been unsuccessful. It is true that Thoma described a diffuse arteriosclerosis in the dog as the result of a chronic experimental aortic insufficiency and that Gilbert and Lion[1] produced scattered sclerotic and calcareous changes in the vessels of animals by injecting bacteria or their toxins. Thickening of the vascular walls has been described also as the result of poisoning animals with lead. These results, however, have been inconstant and lack confirmation. Jores,[2] in his excellent monograph on arteriosclerosis, published in 1903, reached the conclusion, based on a critical review of the literature, that all experimental methods fail to cause lesions similar to those occurring in man. Various endarterial lesions, obliterative or otherwise, as well as diffuse inflammation and atrophy, have been produced by injections of bacteria or their toxins by the application of irritating substances to the perivascular tissues and by ligation and other forms of mechanical injury; but none of these lesions is analogous to true arteriosclerosis.

* This investigation was conducted under a grant from the Rockefeller Institute for Medical Research.

It is a curious coincidence that in the same year in which Jores reached this conclusion Josué[3] described experimental lesions in the aorta of rabbits, essentially similar to those of human arteriosclerosis. These were caused by frequent intravenous injections of adrenalin. With the exception of a few inconclusive experiments of Jores, who gave dogs adrenal tablets in their food in the hope of obtaining lesions due to heightened blood pressure, Josué appears to be the first investigator to attempt the experimental production of arteriosclerosis by the use of the principle of the adrenal gland. His results have been confirmed by Erb,[4] Rzentkowski,[5] Fisher[6] and others. Their reports include but a small group of experiments, and deal for the most part with the late changes, which they describe variously as arteriosclerosis, atheroma and calcification. The principal histologic changes to which they call attention are alteration in the elastica and the infiltration of lime salts.

The importance of a method capable of producing an experimental lesion so closely resembling human arteriosclerosis is apparent. It allows an opportunity to study many of the obscure problems of the disease, as the nature of the primary changes, the sequence of these changes, and the combinations which constitute the fully developed lesion. It was with the hope of elucidating some of these problems that the present investigation was undertaken. The results have been satisfactory beyond all expectation. Vascular changes, capable of throwing much light upon the pathology of arteriosclerosis, and also that of aneurysm formation, have been readily produced. Only a general outline of these will be given at this time, for many of the details of the histologic changes, especially of the process of repair, are so important that they require a more extended study. A consideration of these details is therefore reserved for a future publication, based on a second series of experiments now in progress.

METHODS. Rabbits have received in the veins of the ear repeated injections of a 1:1000 solution of adrenalin. The solution was prepared by a chemist, with due regard to asepsis and chemical purity. Physiologic salt solution was used as a medium. In addition to adrenalin (Parke, Davis & Co.) it con-

tained chloretone in the proportion of one-half of one per cent. and a sufficient amount of hydrochloric acid to make the solution faintly acid.

An initial dose of three minims* and the repetition of the same amount every other day has been the usual procedure, though in some experiments the dose has been gradually increased. Not infrequently the early injections cause death from acute dilatation of the heart and pulmonary edema. Such accidents usually occur after any one of the first seven or eight injections. If the animal survives this period it appears to gain a certain amount of immunity, or, at least, tolerance to adrenalin, so that the dose may be gradually increased during several weeks, until twenty to twenty-five minims may be given every day. This increased resistance to adrenalin has been noted also by Erb and Fisher. The animals have been killed after periods varying from a few days to eight and a half weeks.

For histologic study tissues have been preserved in Zenker's fluid, alcohol and six per cent. formalin; embedded in celloidin; and stained with hematoxylin and eosin, and by Weigert's elastica and Mallory's connective-tissue methods. The Scharlach R. and osmic acid methods have been employed for the demonstration of fat. Sections hardened in Flemming's solution and stained by hematoxylin have been found to be most satisfactory for purposes of general study. By this method the nuclei and areas of calcification stain blue; fat, if present, black. The elastic fibres stand out prominently as light, greenish-yellow, glistening lines, while all other structures are of a faint gray color.

Results. Of twenty animals receiving adrenalin nine succumbed to the acute effects of the drug within fifteen days. These nine represent animals receiving one, three, four, five, seven, and eight injections of adrenalin on alternate days. In some instances death resulted within a few minutes after the injection; in others, after a few hours. The immediate effect of the intravenous administration of adrenalin is collapse with diffi-

* Throughout this report the dose will be given in minims. It would be better, perhaps, to use the values of the metric system, but as Josué and others give the dose in minims or drops we have for purposes of control used the same system of measurement.

cult and rapid respiration. The animal lies on its abdomen, with legs outstretched, and head resting on the table or raised in spasmodic respiratory effort. Death, preceded by severe convulsive movements, may occur immediately. Other animals recover from the immediate manifestations only to succumb after a few hours. Upon postmortem examination the usual picture is acute dilatation of the heart and edema of the lungs, with, not infrequently, small hemorrhages beneath the pleura and pericardium. In one animal hemorrhages were also found in the adrenal. These acute lesions indicate a very serious disturbance in the terminal vascular territories, and are worthy, perhaps, of further investigation; but as our problem has to do only with the histologic changes in the larger vessels, its scope has been limited to that extent. The theoretic conclusions to be drawn from experimental adrenalin edema and their possible application to acute edema of the lung in man have recently been discussed by Josué.[7] In but two of this group of nine animals were changes suggestive of early arteriosclerosis demonstrable. These will be discussed later.

The second group of eleven animals represents those receiving from eight to twenty-eight injections during periods varying from sixteen to fifty-nine days. One of these died on the twenty-fifth day from spinal hemorrhage; another on the forty-sixth day, from unknown cause, three weeks after the cessation of injections; the remaining ten were chloroformed. The aorta in six of these showed marked gross lesions; in the other five it was negative, both macroscopically and microscopically. It is of interest that these five animals were all from the same litter, and each weighed about 750 grams at the time of the first injection. Pic and Bonnamour[8] have come to the conclusion that it is impossible to produce vascular lesions by adrenalin in rabbits weighing less than 2000 grams, and quote in support of this opinion their negative experiments with animals weighing about 1200 grams. That this is not an absolute rule is shown by the fact that the most characteristic and advanced lesions in our series occurred in an animal weighing 870 grams at the beginning and 1020 at the end of the experiment. Otherwise, however, our experience with small animals supports the contention of Pic and Bonnamour.

Attempts to produce lesions in dogs have been unsuccessful. Both old and young dogs have been used. One of the latter, a puppy 2120 grams in weight, received in the ear vein in one month 130 minims of adrenalin in doses rising gradually from four to twenty minims. Although respiratory and cardiac disturbances frequently occurred immediately after injection, thus indicating a definite physiologic action of the adrenalin, no evidence of vascular lesions could be found at autopsy or upon microscopic examination.

Gross Lesions. These appear to be limited to the aorta. The involvement of other arteries, as the brachial, carotid, and renal, which Erb describes, we have not found. The lesions in the aorta are most marked in the thoracic portion, and are seldom found below the cœliac axis or in the first portion of the arch. The earliest change in the vessel wall manifest to the naked eye is a faint longitudinal or irregular grayish streaking of the intima without thickening. This appearance was seen as early as the ninth day in a rabbit which had received five injections. After eight to fifteen injections, especially if the animal is allowed to live for a week or longer after the last injection, very definite lesions are apparent. These consist of irregular, isolated, or confluent areas, usually slightly depressed, of a pearly gray color and almost constantly calcified. The following protocol illustrates this condition:

Rabbit No. 11. Weight, 2300 grams. Killed May 2d after injection as follows: March 29th and 31st, 4 minims; April 2d and 4th, 5 minims; April 6th and 8th, 7 minims; April 10th, 10 minims; April 12th, 12 minims; April 14th, 15th and 16th, 15 minims. *Autopsy:* The aorta is distinctly dilated, measuring 12 mm. in circumference at the arch. Beginning at the origin of the left carotid artery is an irregular patch 37 mm. long, averaging 2.5 mm. in width, and extending in a spiral course along the aorta for a distance of 30 mm. so as to completely encircle it. Along this patch the wall of the aorta is slightly dilated. The media is firm, parchment-like and so distinctly calcified that the vessel cracks in several places when the arch of the aorta is straightened. At one side of this large patch are two very small oval areas of similar structure. There is no atheroma or ulceration. All the other organs are entirely negative.

The late lesions occurring after twenty to twenty-five injections are very well marked. The aorta is more or less distorted, rigid

and non-elastic. Irregular dilatations alternate with elevated brittle areas of calcification. Distinct ulceration with atheroma is not readily demonstrable. Diffuse calcification is not infrequent and small aneurysmal dilatations may be present. The following protocol illustrates the advanced lesions occurring in animals receiving large doses during a considerable period of time:

Rabbit No. 3. Weight, 870 grams. Received first injection of 3 minims in ear vein on November 30, 1904. Similar injections were repeated on alternate days until December 30th, after which date the dose was rapidly increased until it reached 20 minims daily. The animal was killed on January 20, 1905. *Autopsy:* Weight, 1150 grams. The thoracic aorta measures 6 mm. in diameter, is distinctly dilated, irregular in outline, stiff and brittle, although the wall is apparently thinned. This condition extends as far as the cœliac axis, beyond which point the abdominal aorta is apparently normal. On opening the aorta the inner surface of the abdominal aorta above the cœliac axis shows numerous yellowish, slightly raised, calcified patches 1 to 1.5 mm. in diameter, which in the upper portion of the thoracic aorta become confluent. Except in one of the small patches situated in the upper portion of the abdominal aorta there is no evidence of ulceration. All other organs are negative.

The following description from the protocol of a parallel experiment illustrates the tendency to the formation of small aneurysms:

Rabbit No. 2. The aorta averages 3 mm. in diameter except at three places where distinct dilatations occur. The first of these begins 3 cm. below the origin of the aorta and involves the right anterior wall of the aorta for a distance of 2 cm., giving the appearance of a fusiform aneurysm; the diameter of the aorta at this point is 4 mm. A second dilatation, 2.5 cm. in length, occurs in the distal portion of the thoracic aorta and a third involves the abdominal aorta for a distance of 1 cm. immediately below the cœliac axis. On section the inner surface of the aorta shows sharply circumscribed saccular dilatations varying from 1 to 2 mm. in depth and corresponding to the protrusions described above. The walls of these aneurysms contain firm plaques of calcareous material. The intervening aorta shows a number of yellowish-white elevated areas 1 to 3 mm. in diameter. The aorta below the dilatation at the cœliac axis is macroscopically negative.

Histology. In the group represented by the nine rabbits which died during the first two weeks, the vessels of but two showed histologic changes which could be considered the initial lesions of arteriosclerosis. These were animals which had received four and five injections, respectively. The first died on the fifth day

and the second on the ninth day. Scattered through the middle coat of the aorta in each of these are small longitudinal or occasionally irregular, finely granular foci of degeneration. In these areas no nuclei are visible, and the muscle fibres are transformed into a finely granular, almost hyaline material, which stains deeply with eosin. The exact nature of this change is not readily determined, but as the various methods of demonstrating fatty transformation are negative, and those which differentiate elastic fibres show no change in the staining reaction of the latter, the condition would appear to be a simple necrosis limited to the muscle fibres. The elastic tissue has, however, undergone very characteristic morphologic changes, which are found only in the degenerate areas, and are due, presumably, to mechanical influences. In the normal aorta the elastic fibres have a distinctly wavy or curled appearance, and are definitely separated from one another. In the areas described the fibres lose this appearance and become straightened and closely approximated. They are also swollen and occasionally appear to be fused together. Fracture of the fibres is seldom seen at this stage of the process.

A more diffuse lesion of this character was found in an animal killed on the twenty-fourth day after receiving eleven injections. The changes involve the entire circumference of the vessel, sparing to a certain extent, the innermost and outermost portions of the media. In this central zone few or no nuclei can be found, and the altered tissue presents a uniform, finely granular appearance, relieved only by the glistening lines of the elastic fibres. The latter, by selective stain, are seen to be so closely massed together that individual fibres can be distinguished only with great difficulty. On either side of this zone the less degenerated portions of the media show irregular areas, which take the hematoxylin stain in a manner very suggestive of early infiltration with lime salts. There is, however, no distinct calcification and no fracture of elastic fibres.

Lesions of great interest in comparison with the above were observed in two rabbits which had received the same number of injections, but which were allowed to live for ten and eighteen days, respectively, after the last injection. In the aorta of each

are found a few areas of granular necrosis, but for the most part these areas have been altered by infiltration with lime salts. From the topography of the areas of calcification and their relation to the necrotic foci it is evident that the deposition of lime salts follows the necrosis. It would appear, therefore, that the primary degenerative lesions are well advanced by the end of the third week, and that, after this, but one or two weeks' time is sufficient for advanced calcification. The latter may, however, occur much earlier, for in one rabbit, killed on the sixteenth day, small but very definite foci of lime infiltration were present.

In the areas of lighter deposition of lime it is seen that these salts are first deposited between the elastic fibres, an observation which indicates that the destruction of the muscle fibre is the older, and therefore in all probability the primary lesion. In the areas of advanced calcification, although the elastic fibres appear to be completely destroyed by the calcareous transformation, Weigert's stain shows them to be still present, though they stain poorly and are frequently fractured. Not uncommonly at a point of fracture one bundle of fibres overlaps another, the ends being splinted together by an encapsulating mass of lime salts. These fibres are always perfectly straight, except at anglss formed by fracture. A definite relation appears to exist between calcification and fracture of the elastic fibres. Even in areas of the most extensive degeneration no breaks in the elastic fibres have been observed in the absence of calcification, while, on the other hand, they are constantly associated with calcification.

Lesions of this stage show the first evidence of repair. This is indicated by the collection of newly formed cells about the foci of calcification. These cells are closely massed, surrounded by but a slight ring of protoplasm, and appear to be of connective-tissue origin, though it has been impossible to always distinguish between such and the nuclei of smooth muscle fibres. No accumulation of polymorphonuclear leukocytes, or lymphoid cells, has been seen. Of greater interest are the proliferative changes in the intima. These occur only opposite distinct breaks or considerable depressions in the media, and include proliferation of the lining endothelium and, to a greater extent, the subendothelial

tissues. The endothelial cells proliferate to form two or three layers of cells longitudinally arranged, while the subendothelial space, barely visible in the normal aorta, becomes very prominent owing to the presence of closely packed oval nuclei arranged vertically to the lining endothelium. Between the nuclei are delicate, newly formed connective tissue and elastica fibrils. In the late stages the newly formed elastic fibrils are very prominent. In the angle of fracture the nuclei of the media assume a perpendicular arrangement, very striking in contrast to their longitudinal arrangement elsewhere. The entire picture is distinctly that of a compensatory proliferation—an effort to strengthen the weakened point in the vessel wall.

Such are the essential phases of this lesion in the order of their sequence. The more prolonged experiments offer no fundamentally new features, but the combinations of these primary changes in the course of the more extensive involvement of the vessel wall, lead to a complex histologic picture closely resembling advanced human arteriosclerosis. This is seen only in animals which have received gradually increasing doses during a period of seven or eight weeks. The vessel wall becomes greatly thickened, not only by infiltration of lime salts, but also by an extensive repair process, which involves the intima as well as the media. Small foci of complete necrosis, analogous to atheroma and entirely different from the primary degeneration, are also seen in areas in which the elastic fibres are completely destroyed. These present a uniform, finely granular appearance, and stain deeply with eosin. The osmic acid method for fat is negative, and but a few fine droplets are evident after treatment with Scharlach R. About such areas repair takes place, but it is not as active as it is about the masses of lime salts.

The most striking feature of the late histologic picture is the extent of repair in the intima. The latter, with its newly formed connective tissue and elastic fibrils, becomes so greatly thickened that it constitutes in some places a quarter to a third of the entire vessel wall, and offers convincing evidence of the compensatory nature of the repair process.

It is in these late lesions that the small aneurysms are seen.

They occur at points where the elastica is so completely destroyed as to be transformed into an indistinct mass of fractured granular and fused fibres. The transition from normal to necrotic fibres is always sharp and distinct, and marked by complete fracture of all elastic tissue. It is worthy of note that in the thinned wall of these aneurysms the degree of calcification is, as a rule, less marked than elsewhere. The adventitia is compressed, but otherwise unaffected.

The changes in other organs include enlargement of the heart, edema, and congestion of the lungs, degenerative changes in the liver and kidney and occasionally, also, in the heart and skeletal muscles. In one case degenerative lesions were found in a nerve ganglion adherent to the aorta. It was thought that these changes might have some etiologic relation to the vascular lesion, but a thorough study of all our material failed to reveal lesions in other animals or in other ganglion of the same animal. The affected ganglion was in the adventitial tissue of an aneurysmal dilatation, and the effects of pressure and disturbed blood supply were sufficient, apparently, to account for the changes observed.

The Mode of Action of Adrenalin. The manner in which adrenalin produces these lesions is a matter of widely varying opinion, and, unfortunately, one which at present cannot readily be determined by experimentation. Until we know more about the toxic action of adrenalin and can distinguish between the lesions due to this action and those due to increased blood pressure, and especially between its direct and secondary effect on the bloodvessels, we can hope for no elucidation of this problem. Drummond,[9] who has recently made a thorough study of the histologic lesions caused by adrenalin, divides all into those due to toxic action and those due to increased blood pressure. It is obvious that such a classification is difficult, for it is impossible to determine to what extent degenerative lesions are due to interference with the circulation through action on the bloodvessels.

A discussion of the variety of ways in which adrenalin might act, directly or indirectly, to cause degenerative changes in the media of the aorta would, in the present state of our knowledge, be of little value. The difficulty of reaching definite conclusions

is illustrated by the diversity of opinion expressed by those who have previously produced the lesions here described. Josué believes them to be due to a combination of a specific toxic influence and the increased blood pressure. Rzentkowski believes in the latter influence only. Erb ascribes an important influence to disturbance of the vasa vasorum. Fisher thinks that, aside from the increased blood pressure, disturbances of metabolism play an important part. Lissauer[10] believes that the toxic influence is the most important factor, but offers no explanation of its mode of action.

No definite conclusion can be drawn from our own experiments. The observation that the earliest changes occur in the media and are apparently primary in the smooth muscle fibres suggests, in view of the well-known physiologic action of adrenalin on this tissue, a direct and selective toxic action; but the absence of similar lesions in vessels other than the aorta does not support this view. For the same reason, and also because of the absence of changes in the adventitia, the vasa vasorum theory appears to be untenable. On the other hand, if we assume, as is very probable, that the changes in form and arrangement of the elastic fibres are due to the same factor which causes the destruction of the muscle cells, and are not secondary to the latter, we have a strong argument in favor of the influence of a greatly heightened blood pressure, for it is conceivable that these diffuse changes might result from a continued severe stretching of the vessel wall. Although it is impossible to determine to what extent the primary changes are mechanical and to what extent toxic in nature, it is certain that some of the secondary changes, as the fracture of elastic fibres and the formation of aneurysms, are largely due to mechanical factors. These problems, however, must be settled by other methods of experimentation.

Comparison of the Experimental Lesions and those Occurring in Man. If due allowance is made for the difference in size between the aorta of the rabbit and that of man it must be admitted that the lesions produced in the former as the result of the administration of adrenalin are analogous to those occurring in human arteriosclerosis. All the essential processes are represented, and, considering the delicate character of the

wall of the rabbit's aorta, the lesions are relatively as extensive and cause the same degree of deformity. It appears, therefore, justifiable to term this condition experimental arteriosclerosis. The only objections which can be made to such a conclusion are that, compared with the human lesion, the degree of atheroma is insignificant, and is limited to the media. Extensive atheroma, however, cannot be expected in a vessel wall as thin as the rabbit's aorta; and, moreover, in none of these experiments has a period of time, sufficient for the occurrence of degeneration in areas of excessive intimal proliferation, elapsed. More prolonged experiments will yield, it is to be hoped, lesions more conclusive in this respect.

In the light of the information gained from the study of these experimental lesions it would be desirable, perhaps, to critically discuss the various theories concerning the nature of arteriosclerosis, and especially the character and sequence of the histologic changes. Such discussion, however, does not come within the scope of this communication, and many minor points must be determined before comparisons are justifiable. It is sufficient for the present to point out the strong support afforded Thoma's view that the primary lesion of arteriosclerosis occurs in the media, and is, essentially, the result of injury to the elastical and that the changes in the intima constitute a repair process, the object of which is to compensate for the weakened media and the widened lumen.

References.

1. Gilbert, A., et Lion, G. Note sur l'athérome artériel expérimental, Arch. de méd. expér. et d'anat. path., 1904, xvi. 73.

2. Jores, L. A. Wesen und Entwickelung der Arteriosclerose, Wiesbaden, 1903.

3. Josué, O. Athérome aortique expérimental par injections répétées d'adrenaline dans les veines, La presse médicale, 1903, xi. 798.

4. Erb, W., Jr. Ueber experimentell erzeugte Arterienerkrankung beim Kaninchen, Verhandl. des Kongress f. innere Med., 1904, xxi. 110.

5. v. Rzentkowski, C. Atheromatosis Aortæ bei Kaninchen nach intravenösen Adrenalin injectionen, Berl. klin. Wochenschr., 1904, xli. 830.

6. Fisher, B. Experimentelle Arterienerkrankungen durch Adrenalininjectionen, Münch. med. Wochenschr, 1905, lii. 46.

7. Josué, O. Pathogénie de certains cas d'edéme aigu du poumon, La presse médicale, 1905, 1231.

8. Pic, A., et Bonnamour, S. Contribution a l'étude du déterminisme de l'athérome aortique experimentell, C. R. de la Soc. de biol., 1905, lviii. 219.

9. Drummond, W. B. The Histologic Changes Produced by the Injection of Adrenalin Chlorid. The Journal of Physiology, 1904, xxxi. 81.

10. Lissauer, M. Experimentelle Arterienerkrankungen beim Raninchen, Berlin. klin. Wochenschr., 1905, xlii. 675.

PERIPHERAL PHLEBOSCLEROSIS.

By C. F. MARTIN, B.A., M.D., and J. C. MEAKINS, M.D.,
of Montreal.

(From the Medical Clinic of the Royal Victoria Hospital.)

Since the interesting observations of Sack, a pupil of Thoma, it has, I think, been generally conceded that sclerosis of the veins is to be regarded as a system disease, analogous in origin, in topography and in pathologic findings to arteriosclerosis. It is to the pathologist chiefly that the subject has been of interest, for clinicians have shown it but scant attention. Lobstein, who first gave it the name of phlebosclerosis, regarded it as a senile degeneration, and noted at the same time its frequency as a local condition.

So far as its etiology is concerned, it was held by Sack to be a general disease of the vascular system, induced by disturbances of general nutrition, which caused a weakening of the media. As in the case of arterial disease, so here the weakening resulted in dilatation of the vessels and compensatory thickening of the intima. The same causes which Thoma regarded as incident to arterial disease he claimed were equally effective in inducing the disease in the venous system.

Bernard Fischer, a pupil of Jores, has regarded phlebosclerosis as primarily of inflammatory origin, thus following the theory of Koestner; and in his sections he found collections of small round cells in proof of his contention. It was further insisted upon that a definite relationship existed between diseases of the arteries and those of the veins, and that the degree of sclerosis in the individual veins was greater in proportion to the development of the arterial disease. This, however, was not an

infallible rule, for even without the usual causes and in the absence, too, of arterial disease a phlebosclerosis was found not to be altogether uncommon, though in such instances the degree of change in the veins was considered too slight to interfere seriously with the theory of its analogy to sclerosis of the arteries. In all these conditions both arteries and veins suffer from the diffuse form of sclerosis. Sack indeed believes that in all cases of venous sclerosis one could distinguish between the diffuse and the nodose form, the latter being of the nature of an endophlebitis, while the diffuse is secondary to the process similar in the arteries.

Perhaps the most striking feature in connection with phlebosclerosis is its predilection for *peripheral* veins, and we would emphasize this fact in our findings that the presence of thickened veins, especially in the periphery, is of far greater frequency than is generally supposed; and more especially is this the case in young adults, both male and female, without the presence of associated arterial disease.

That such a condition might be fairly common in the young was suggested from an examination of one of our cases, first observed by Dr. W. W. Francis, resident physician of the Royal Victoria Hospital. The patient was a boy, aged eighteen years, who had entered the hospital for acute rheumatism, and in whose history, present illness or general condition there was nothing to account for the morbid state; nor did his occupation or habits throw any light upon the sclerosis. The physical examination, however, revealed the veins in both upper and lower extremties so thick, so hard and cord-like as to suggest abnormally sclerosed arteries rather than veins. Those chiefly affected were the internal saphenous, the popliteal, the brachial and the ulnar. It was therefore with some interest that subsequently an examination of the young adults then present in the hospital revealed the fact that varying degrees of the condition were present in more than 60 per cent. of the patients examined. The accompanying table (see pages 528 and 529) would indicate the findings in this series of young adults examined for this purpose, those only being noted in whom the sclerosis was present.

The striking features observed from the table are, briefly, as follows: The patients noted are nearly all under thirty-five years

of age. Males were chiefly observed, for the condition is much less common in females. It will further be seen that in most of these individuals arterial disease is either absent or very slightly present, and that in nearly all the cases there was nothing either in the past history or the present malady which would account for the condition. Locally, there was no obstruction or stagnation which could suggest a cause, nor were the occupation and habits such as to afford any clue.

As everyone knows, wherever local stasis occurs, even without arterial degeneration, there is a tendency to sclerosis in the veins, and indeed such conditions have been repeatedly observed, with pregnancy, with ascites, and with various cardiac lesions. In our own series, however, no such local cause could be detected, and the explanation is not readily found. Certainly, one can scarcely accept the contention of Sack that such few instances of the kind that he saw, where the peripheral sclerosis had no accountable cause, were to be explained on a basis that the patients examined were from hospital practice only. A number of the patients examined by us, apart from those mentioned in the table under similar conditions, were taken from sources entirely outside of hospital practice.

Sections were taken from the veins in nine of our cases, mainly from the internal saphenous, which was the one most commonly affected. These were variously stained with hematoxylin, with Mallory's stain, Unna's, and Weigert's, and a few also were treated with Sudan III. As in the observations of Sack, so in our own sections, the changes were rarely of a degenerative nature ; on the contrary, there was chiefly a hyperplasia of the connective tissue, more especially in the intima, which was seen to protrude irregularly into the lumen of the vessel, and showed a loose structure with little elastic tissue, comparatively few cells, and for the most part little or no hyaline degeneration. The media was also affected similarly, and in some cases so intimately mixed were the conditions of hyperplasia in intima and media that it was quite impossible to determine the limitations of the individual layers. In a few sections, however, the separation was most marked. The specimens stained with Sudan III. gave no evidence whatever of fatty change.

Theories as to the causation of this frequent condition would seem to lie between the inflammatory nature of the malady, as

PHLEBOSCLEROSIS.

+ = present. 0 = absent. v = specimen examined microscopically.

No.	Case No.	Diagnosis.	Age	Occupation.	Lues.	Recent infections	Other diseases or intoxications.	Arterio-sclerosis.	Alcoholism	Varicose veins.	Internal saphenous.	External saphenous.	Cephalic.	Basilic.	Radial.	Ulnar.	Median	Specimen examined.
1	8448	Acute rheumatism	18	Elevator boy	0	.....	.....	0	0	0	+	+	+	+	+	+	+	0
2	9532	Typhoid fever	28	Electrician	0	Infected knee, rheumatism	Pleurisy, pneumonia, tuberculosis, mumps, measles	0	Slight	0	+	+	+	+	+	+	+	v
3	9619	Acute rheumatism	23	Valet	0	Tonsillitis	Measles	Very slight	Slight	0	+	+	+	+	+	+	+	v
4	9757	Tuberculous meningitis	19	Farmer	0	.....	.....	0	0	0	+	+	+	+	+	+	+	v
5	9800	Pleurisy & tuberculosis	24	Clerk	0	Appendicitis	Measles	0	0	0	+	+	0	0	0	0	0	v
6	9801	Pleurisy	30	Laborer	present	Typhoid fever	.....	0	0	0	+	+	0	0	0	0	0	v
7	9803	Pleurisy	28	Boxmaker	0	.....	Measles	0	0	0	+	+	0	0	0	0	0	v
8	9807	Pulmonary tuberculosis	37	Bookkeeper	0	Gonorrhea	Children's diseases (?)	0	Slight	0	+	0	0	0	0	0	0	v
9	9694	Cerebral tumor	26	Office work	0	.....	Measles	0	Slight	0	+	0	0	0	0	0	0	0
10	9757	Meningitis	22	Painter	0	Typhoid rheumatism	Measles	0	0	0	+	+	0	0	0	0	0	0
11	9621	Acute rheumatism	35	Factory hand	0	.. ..	.....	Very slight	0	Slight	+	+	+	+	+	+	+	0
12	9691	Acute rheumatism	27	Student	0	Influenza	Jaundice	0	0	0	+	0	0	0	0	0	0	0
13	9678	Arthritis deformans	29	Designer	0	Rheumatism twice	....	0	0	0	+	0	0	0	0	0	0	0
14	9739	"Febricula"	19	Barber	0	Gastroenteritis	Chronic gastritis	0	0	0	+	0	0	0	0	0	0	0
15	9999	Intestinal obstruction	31	Telegraph operator	0	.....	.....	0	0	0	+	+	+	+	+	+	+	0
16	10050	T. B. C. peritonitis	20	Student	0	.....	.....	Very slight	0	0	+	+	0	0	0	0	0	0

17	10078	Periureteral abscess	29	Woodworker	0	Gonorrhea	.....	0	0	0	+	+	0	0	0	0	0	0
18	10129	Infected hand.	26	Shoemaker	0	.....	.....	0	0	0	+	+	+	0	0	0	0	0
19	10143	Appendicitis	23	Carpenter	0	Typhoid fever	.....	0	0	0	+	+	0	0	0	0	0	0
20	9776	Pneumonia.	21	Chemist	0	Tonsillitis, bronchitis	Measles	0	Slight	0	+	+	0	0	0	0	0	0
21	10126	Appendicitis.	44	Jobbing	0	.....	Furunculosis	Very slight	0	0	+	0	+	0	0	+	0	0
22	9645	Typhoid fever	29	Fireman	0	Acute rheumatism	Measles	Very slight	Very slight	0	+	+	0	0	0	0	0	0
23	9641	Pneumonia & pleurisy	28	Architect	0	.....	Chorea	Slight	0	0	+	+	0	0	0	0	0	0
24	9687	Acute rheumatism	50	Machinist	0	Influenza	Pleurisy	Slight	Excess	0	+	+	0	0	0	0	0	0
25	9603	Acute rheumatism	42	Cook	0	Jaundice	Whooping-co'gh, measles	Very slight	Slight	0	+	+	0	0	0	0	0	v
26	9591	Chronic nephritis	50	Insurance agent	0	Typhoid	Gonorrhea	Marked	Excess	0	+	+	+	+	+	+	+	v
27	9732	Mediastinal tumor	45	Housewife	0	.....	Measles, scarlatina	0	0	0	+	+	+	+	+	+	+	0
28	9770	Multiple endocarditis	20	Servant	0	Rheumatism	.....	0	0	0	+	+	0	0	0	0	0	0
29	9831	Gastric ulcer	24	Servant	0	Gastric ulcer	Rheumatism	0	0	0	+	+	0	0	0	0	0	0
30	9826	Typhoid fever	21	Clerk	0	.....	.....	0	0	0	+	+	0	0	0	0	0	0
31	9786	Multiple endocarditis	35	Housewife	0	Rheumatism	.....	0	0	0	+	+	0	0	0	0	0	0

described by Koestner and others, the degeneration theory of Thoma, and, thirdly, the purely mechanical process, of which more will be said later.

It was not our good fortune, however, to find in any of the peripheral veins examined evidence of an inflammatory change, as described by Fischer. Primary degeneration of the media, moreover, was certainly not a prominent feature. It is rather remarkable, however, that Sack, in his hundred cases examined postmortem, found among the peripheral veins no evidence of disease in the radial and ulnar veins, a circumstance for which he accounted on mechanical grounds. According to his belief, the frequent slight and gentle motions of the arms assisted both the more even propulsion of the blood and the regulation of the vascular tone. Then, too, the lesser resistance in the thorax to the onflow of venous blood would contribute to spare those veins, while, on the other hand, the veins going to the abdomen met with marked obstruction, even under normal conditions, from the ordinary intra-abdominal pressure.

The frequency of peripheral venous sclerosis in the lower extremities, however, gives rise to the natural inquiry as to whether, after all, this so-called sclerosis is, indeed, of a pathologic nature, and, if so, why should the changes be so marked in the peripheral veins alone? For such, indeed, is the case, and in the postmortems on subjects with peripheral sclerosis no visceral venous sclerosis was evident.

It is a well-recognized fact that in the arterial system various physiologic processes are accompanied by hyperplasias, due to physiologically active causes, as is seen, for example, in the umbilical arteries after birth, and in vessels from the pregnant uterus. Jores and Fischer make, therefore, the following distinction: Where regular, even thickening of the arteries occurs in the intima, there we have merely a physiologic change, and where, on the other hand, the thickening is uneven, irregular and inclined to be nodular, one may speak of a pathologic sclerosis. Thoma's examinations of individuals over thirty-five showed thickened veins to be frequent, but in such cases, he said, the thickening was always regular. Our own cases, however, in still younger adults, scarcely coincided with these findings, for the thickened intima was in many instances quite irregu-

lar, though, as already stated, there was but little evidence of true inflammation. Accepting Jores' distinction, our cases of peripheral sclerosis should certainly be regarded as pathologic.

To epitomize the findings:

1. The condition of peripheral phlebosclerosis is extremely common.

2. It is much more common in young people than is generally believed.

3. Its presence in the absence of arteriosclerosis is very frequent.

4. Sections show, as a rule, absence of signs of inflammation and of marked degeneration.

5. There are not present most of the usual causes often associated with arterial disease—viz., toxic, infective, etc.

6. The essential change found is proliferation of cells of the intima and of connective tissue in the media.

7. The condition is allied rather to functional hyperplasia than to chronic inflammation.

Occurring, as it does, peripherally, and again more commonly in the lower than in the upper extremities, one would reasonably be inclined to regard the affection as largely the result of *mechanical conditions:* Strain on the vascular walls from the posture, even though this be somewhat relieved by the valves in the vein, would make itself felt in a similar way as ordinary stasis from obstruction, though to a less degree. Occupations involving the erect posture and greater use of the extremities, and leading to fatigue, more especially in those whose nutrition is poor, and who, therefore, lack somewhat the additional support which the tissues necessarily give to superficial veins. The condition is certainly *not a toxic nor an inflammatory one,* as may be concluded from its great frequency and from the absence of the usual histologic changes; nor can it be necessarily always related to arterial disease. It is doubtless rare to find a man with arteriosclerosis without some similar change in the veins; yet in our most marked case of arterial disease in a man, aged fifty years, dead from chronic Bright's disease, the peripheral veins alone showed thickening, those elsewhere being practically free from signs of degeneration or of hyperplasia.

The presumable etiology may be gathered from a reference to

Dr. Adami's Middleton-Goldsmith lecture on the relation of inflammation to fibrosis by applying his remarks to peripheral veins under the above mentioned conditions. "We have to deal with a stimulus rather than injury to the cells of the intima, and may see in the fibrous hyperplasia a response to a physiologic stimulus rather than a reaction to injury. . . . Were some irritant discovered directly capable of inducing the hyperplasia of the intima, the case might present a different facies." In the absence of this factor in cases of peripheral venous sclerosis one should regard the hyperplasia as functional in origin, the result of mechanical forces, and a condition which, even in youth, is far more commonly present clinically than is, we believe, usually recognized.

LITERATURE.

E. Sack. Ueber Phlebosklerose und ihre Beziehung zur Arterio-Sklerose, Virchow's Archiv, Bd. cxii.

B. Fischer. Ueber Entzundung, Sklerose und Erweiterung der Venen, Inaug. Diss. Jena, 1900.

J. G. Adami. On the Relationship between Inflammation and Sundry Forms of Fibrosis, Medical Record, 1896.

DISCUSSION.

DR. WELCH: I should like to ask Dr. Pearce how far the points of stricture correspond with the diagnosis of arteriosclerosis? As is well known, it separates the fibrous thickening of the intima in the cases called obliterative arthritis and are not at all identified with cases of sclerosis. How far the changes in the rabbit confirm these views of Jores of the established separation of the media into these two groups—one of a fibrous productive inflammation and the other of a distinct arterioscleroiss.

DR. MELTZER: I should like to ask if the smaller animals have been examined for lesions. We have had animals kept seven months in which the superior cervical ganglion was removed and found that the effect was pronounced. These animals received quite a large number of injections, the effects getting less. In animals killed the next day no change took place.

DR. PEARCE: I have compared these experimental lesions with the various vascular lesions described by Jores and others, and find no resemblance to the different forms of obliterating endarteritis. The lesions, on the other hand, very closely resemble those of Jores' second group; that is, true arteriosclerosis. Concerning Dr. Welch's other question, I may say I have been unable to

demonstrate to my own satisfaction a splitting of the elastica similar to that which he mentions.

Dr. Meltzer has asked if vessels other than the aorta are involved in this experimental lesion. It is possible, but in all our animals we have made a careful examination of other vessels and have not found lesions.

The lesions of the ganglia we found in one of the animals recently killed. I have not had time since to look for similar changes in all the other animals.

ON THE USE OF OPIUM IN MYOCARDITIS, WEAK HEART AND DILATED HEART.

By J. H. MUSSER, M.D.,
OF PHILADELPHIA.

There are sound clinical reasons for the belief that opium is a tonic in cardiac debility. Who has not seen the flagging heart of shock induced by pain or other depressive measures brought up by morphin? Who will not prescribe this drug in the sudden heart failure of myocarditis—the asystole with the accompanying edema of the lungs of this affection? Who does not give it in rheumatism for its tonic cardiac effect? I plead for the continuous use of opium or morphin also in myocarditis to prevent angina pectoris, or to lessen the effect or defer the dreaded asystole. I have had patients take for months and months small doses of the deodorized tincture or the extract of opium, thereby checking waste, reducing the susceptibility to peripheral sensations which fret an irritable heart, replacing exciting stimulants, as alcohol and strychnin, calming a perturbable nervous system and lessening the necessity for food to the relief of digestion, metabolism and elimination.

In cases of weak heart after exhausting disease, after prolonged mental and physical pain and without organic lesion of valves or muscle opium is of advantage.

In cases of failing compensation, with the onset of stases, the heart is supported, especially if the unfortunate possessor is an impressionable subject who frets and fumes because of the ordinary irritations of life.

In the gradual engorgements from myocardial dilatation, in chronic parenchymatous nephritis and in arteriosclerosis it is of

value. If the patient is hypochondriacal or hypersensitive the second daily dose of opium invites sleep and induces a feeling of well being.

The dyspnea of myocarditis is relieved or prevented by continuous small doses of morphin for a very long time. I have seen a form or stage of myocarditis with restlessness, Cheyne-Stokes breathing, dyspnea and rapid pulse helped by continuous doses of opium. The tachycardia of Graves' disease is relieved, and in three of my instances it appeared to contribute to the cure of the disease. In the nervous and irritable subjects opium is almost necessary to induce comfort.

DISCUSSION.

Dr. Fussell: I should like to support what Dr. Musser said. I have seen the good effects of opium in myocarditis frequently. In two cases it was particularly marked; one was a lady of seventy-eight years, who had an attack of pneumonia. Of course, she had more or less myocarditis. On one occasion, after the subsidence of her acute pneumonia, she suffered from severe enteritis. There was a considerable amount of albumin, numerous casts, with an extremely rapid heart, and on account of her extreme restlessness and dyspnea we gave her hypodermically morphin $\frac{1}{10}$ or $\frac{1}{12}$ of a grain, with the happiest results. The urine, which was down to 24 ounces in the twenty-four hours, rapidly ran up and the patient recovered entirely. We continued this use of morphin throughout several weeks. Morphin seemed to be the one drug that saved her life. In the first case I used morphin it was in the beginning of my practice of medicine. A woman with heart disease came under my care in a desperate condition; she had apnea, edema, etc. I thought to make her die easy I should give her a hypodermic of morphin, but instead of dying she rapidly improved under the use of this drug.

Dr. Robinson: I should like to make this one point which I consider an important one. I think we agree with what Dr. Musser has said, that in numerous cases of heart failure in acute disease opium or some other drug of like therapeutic effect is invaluable. But there are instances which, clinically, we have all seen in which a relationship exists between disease of the heart and a disease of the kidneys, and where we feel apprehension that elimination through the kidney will be interfered with by giving opium in any form. When we thus fear that we may rather promote the early death than the recovery of patient, I find the question of the use of opium very difficult to determine.

For a good many years past I have practically settled the matter by the condition of the pupil. If the pupil is at all dilated I feel that we can give opium of some form with decided advantage. If we give injections of morphin when the pupil is contracted the result will often be different from what has been hoped for.

Dr. Jacobi: In behalf of those in the practice of medicine I should say amen in regard to the remarks made by Dr. Musser. There are exceptions to every thing, and, as Dr. Robinson says, it is always good to use caution. There is only one thing I should add. Just as important and useful as opium is in most of these cases, just as harmful is the use of strychnin, which is being used so much. I think there is no remedy which does greater harm in the average case of myocarditis than strychnin.

Dr. McPhedran: Of course, all are aware that several years ago Clifford Allbutt advised the use of morphin in cardiac failure, and that no heart tonic is so effective in giving relief. The use of small doses of opium in chronic cases as recommended by Dr. Musser is not so well known. The advice will, I am sure, bear good fruit.

THE CONSTITUENT OF THE BILE CAUSING PANCREATITIS.

By SIMON FLEXNER, M.D.,
OF NEW YORK.

The study of which this note forms a brief report was undertaken to determine the constituent of the bile which causes inflammation of the pancreas. In the course of my studies on hemolytic substances I was led to consider the cytotoxic action of biliary salts, and from this consideration I formed the notion that possibly those salts are the chief agents in bile producing cell death in the pancreas. The test was easily carried out. The first experiments, which were made with a commercial taurocholate of sodium, were convincing, but as this salt was not pure the subsequent experiments were made with the total bile salts prepared from dog's bile. These salts were easily gotten in a perfectly white and practically pure condition.

The experiments were made by dissolving the bile salts in physiologic salt solution so as to reproduce a strength approximating that of the salts in normal bile. The solutions were injected directly into the main duct of the pancreas, and the duct, as a rule, was tied. When amounts of the solution equalling five cubic centimeters were injected the results were fatal frequently within twenty-four hours. Death sometimes occurred within twelve hours; one dog succumbed in six hours.

The effect of the injection begins to manifest itself almost immediately. The artificial edema is quickly followed—within a few minutes, indeed—by a brownish, mottled discoloration of the organ. This change is due to the action of the bile salts upon the blood and bloodvessels of the injected areas. The dis-

colored areas increase continuously in the next minutes and approximate each other more and more closely.

It is clear from the condition found after death that the bile salts act injuriously upon the parenchyma of the pancreas, upon the bloodvessels, and upon the blood. The earliest visible change is in connection with the bloodvessels, which are rendered quickly pervious to the blood, and with the blood, which is changed directly, it comes into contact with the solution of bile salts. The action of the salts on the blood is, of course, from without, but the rate of diffusion into the coats of the vessels must be rapid to bring about in a moment the severe structural changes described.

Eventually the appearances characteristic of experimental pancreatitis and fat necrosis are produced. The type of inflammation which tends to appear is the acute hemorrhagic, but other forms of inflammation, depending upon the intensity of action and secondary conditions, may arise. In one instance a gangrenous condition, associated with a large cavity in the lesser omentum containing necrotic and putrefactive pancreatic tissue, was produced. The necrotic walls of this cavity were incrusted with fat necrosis, and communication existed between this omental cavity and several necrotic, hemorrhagic and softened putrefactive foci in the pancreas.

Control experiments were made with the constituents of the pancreas from which the bile salts had been removed. Since the salts were obtained by extraction with alcohol the albuminous constituents and a part of the coloring matter were precipitated in a state allowing easily of resolution. The mucigenous and other parts of the precipitate were dissolved or resuspended in physiologic salt solution and injected into the pancreatic duct. No acute inflammation resulted.

Since in general the injurious influence of bile salts upon the pancreas is greater than the full bile, and since the bile constituents deprived of bile salts are without marked injurious action, it seems to follow that the bile salts are modified in their activity by reason of association with the non-injurious fractions of the bile. This probability was easily open to verification.

Bile salts were dissolved in salt solution and in the resuspended precipitated constituents, and injected into different dogs at the same time. The results were conclusive. The dog receiving the bile salts in simple solution showed more severe lesions than the one which received the reconstructed "full" bile.

The manner of this modification of injurious activity was studied. It was established that while the precipitated fraction of the bile is not capable of setting up inflammation of the pancreas, yet it has the power to reduce the action of the bile salts. It was of course conceivable that some directly antagonistic substance existed in the precipitated portion, but it was also possible that the restraining action was due to the colloidal nature of the precipitated material. Strong alcohol throws out of the gall-bladder bile the mucin and other albuminous constituents, and when resuspended these give to the solution its colloidal character. To determine which of these factors was the active one resort was had to other "bland" colloidal substances, since the detection directly of antagonistic substances in view of their purely hypothetic nature was surrounded with great difficulties. It was, however, found that such simple colloids as gelatin and agar-agar restrained the action of bile salts quite in the manner of the colloidal constituents of the bile itself.

The demonstration that bile sets up inflammations of the pancreas by virtue of the bile salts contained in it is not surprising in view of our knowledge of the cytotoxic property of the biliary acids; it is, indeed, in full harmony with that knowledge. But it is of interest to understand the mechanism of the action of bile in this respect, and especially the restraining action of the biliary colloids. There are not a few inflammatory affections of the pancreas which have not yet received an adequate explanation. Among this obscure group instances of acute inflammatory lesions of the organ of more or less circumscribed extents occur, and other examples of partial or general sclerosis of the organ unassociated with obstruction of the ducts, or general sclerosis of the viscera, exist. Opie has shown by his important discovery that bile entering the pancreatic duct may set up active acute inflammation. It would seem from the facts of the preceding

experiments that the degree of this inflammation, and possibly its extent also, might be controlled by the relative quantities of biliary salts and colloids in the bile at the moment of its escape into the pancreas. Since inflammation of the biliary ducts and gall-bladder tend to render the bile richer in colloids, and since much fluctuation of the colloidal and biliary saline constitution must occur under these pathologic conditions, it is conceivable that a wide variety of effects might be caused by the escape of bile of such different compositions into the pancreas.

INDEX.

Acetanilid, chronic poisoning by, 47, 388
Acromegaly associated with symptoms of myxedema, 93
Acute non-tuberculous pneumonia, 173
Address of President, 1
Ailurophobia and the power to be conscious of the cat as near, when unseen and unheard, 4
Arteriosclerosis, experimental, 513

Bacterial toxins and immunity, 265
Barker, L. F., lymphatic leukemia, 263
metabolism in leukemia, 322
some considerations on proteid diet, 181
Bile, constituent of, causing pancreatitis, 537
toxicity of, studies on, 196
Billings, F., stone in kidney, 141
treatment of cardiospasm, 327
Bradycardia, cases of, 158

Cabot, R. C., chlorids in nephritis, 443
Calcareous degeneration, 470
Cardiospasm, treatment of, by new esophageal dilator, 324
Carroll, J., toxicity of bile, 238
Cat-fear and consciousness of cat-presence, 4
Cerebrospinal meningitis, herpes complicating, 167
Chlorid exchanges in nephritis, 428
Chylous and chyliform effusions into the serous sacs, 142
Cirrhosis of liver, 356
Cohen, S. S., acromegaly associated with symptoms of myxedema, 95
chronic uremia, 237
hematemesis and gastric ulcer, 348
relation of intestinal disorders to diabetes mellitus, 467
Cohoe, B. A., some considerations on proteid diet, 181
Collins, J., chlorids in nephritis, 444
Constituent of the bile causing pancreatitis, 537

Danforth, I. N., stone in kidney, 139, 140
Diabetes mellitus, 446
Dock, G., sphygmograms from two cases of bradycardia, 158

Edsall, D. L, acute leukemia with some striking clinical features, 278, 294, 323
chlorids in nephritis, 441
Effusions, chylous and chyliform into the serous sacs, 142
Elimination of chlorids in nephritis, 431
Endocarditis, chronic, fever in, 70
gonorrheal septicemia and, 391
Epigastric linea alba hernia as a little recognized source of abdominal pain and of gastric symptoms, 96
Esophageal dilator, new, 324
Ewing, J., intrapleural lipoma, 66
metabolism in leukemia, 322
toxicity of bile, 237
Exophthalmic goiter, 352
Experimental arteriosclerosis, 513

Fever in chronic endocarditis, 70
Fife, C. A., chlorid exchanges in nephritis with special reference to the dechloridation treatment, 428
Fitz, R. H., intrapleural lipoma; acute pericarditis; pericardial exploration, 57, 67, 68
Flexner, S., constituent of the bile causing pancreatitis, 537
Forchheimer, F., case of lymphatic leukemia, 262
intrapleural lipoma, 67
stone in kidney, 141
Fussell, M. H., use of opium in myocarditis, 535
Futcher, T. B., xanthelasma and chronic jaundice, 241, 253

Gastric ulcer, hematemesis from, 339
Goiter, exophthalmic, 352
Gonorrheal septicemia and endocarditis, 391
Greene, C. L., acromegaly associated with symptoms of myxedema, 93
rhythmic lateral displacement of the heart as a sign of unilateral pleuritic exudate, 89
Griffith, J. P. C., intestinal perforation in typhoid fever in early life, 328

Heart, rhythmic lateral displacement of, 89
neurotic, some phases of, 29
use of opium in diseases of, 534
Hematemesis from gastric ulcer, 339
Hemophilia, contribution to, with special reference to the joint symptoms of the disease, 15
Hernia in linea alba, 96
Herpes complicating cerebrospinal meningitis, 167
complicating pneumonia, 165

Herrick, J. B., chronic acetanilid poisoning, 388
Howard, W. T., frequency and etiology of acute non-tuberculous pneumonia in a general hospital, 173
Howard, W. T., further observations on the relation of lesions of the Gasserian and posterior root ganglia to herpes occurring in pneumonia and cerebro-spinal meningitis, 165
Hyperchlorhydria, use of nux vomica in, 193

Intestinal perforation in typhoid fever in early life, 328
Intrapleural lipoma, 57
Irons, E. E., chronic acetanilid poisoning, 388

Jacobi, A., chlorids in nephritis, 444
fever in chronic endocarditis, 86
intestinal perforation in typhoid fever, 338
use of opium in myocarditis, 536
xanthelasma and chronic jaundice, 253
Jaundice, chronic, 241

Kelly, A. O. J., chlorid exchanges in nephritis with special reference to the dechloridation treatment, 428, 445
exophthalmic goiter, 355
fever in chronic endocarditis, 84
nature and lesions of cirrhosis of liver, 356
relation of stomach disorders to diabetes mellitus, 467
Kidney, stone in, 108
Kinnicutt, F. P., chlorids in nephritis, 441
contribution to hemophilia with special reference to the joint symptoms of the disease, 15
fever in chronic endocarditis, 88
hematemesis from gastric ulcer, 348
Klotz, O., calcareous degeneration, 470
Kober, G. M., chlorids in nephritis, 443

Leukemia, acute, 278
lymphatic, in a child, 254, 262
metabolism in, 294
Linea alba, hernia in, 96
Lipoma, intrapleural, 57
Liver, cirrhosis, 356
Low, H. C., case of lymphatic leukemia in a child, 254
Lymphatic leukemia in a child, 254, 262

McPhedran, A., use of opium in myocarditis, 536
MacCallum, W. G., pathologic anatomy of exophthalmic goiter, 352, 355

Martin, C. F., peripheral phlebosclerosis, 525
Meakins, J. C., peripheral phlebosclerosis, 525
Meltzer, S. J., arteriosclerosis, 532
bacterial toxins and immunity, 277
chlorids in nephritis, 442
studies on the toxicity of bile, 196, 238
Metabolism in leukemia, disturbances of, 278, 294
Miller, J. L., elimination of chlorids in nephritis, 431
Mitchell, J. K., fever in chronic endocarditis, 85
Mitchell, S. Weir, ailurophobia and the power to be conscious of the cat as near, when unseen and unheard, 4
Morse, J. L., case of lymphatic leukemia in a child, 254, 264
Musser, J. H., hematemesis from gastric ulcer, 350
metabolism in leukemia under the influence of the *x*-ray, 294
use of nux vomica in hyperchlorhydria, 193, 195
use of opium in myocarditis, weak heart and dilated heart, 534

Nephritis, chlorid exchanges in, 428
elimination of chlorids in, 431
Neurotic heart, some phases of, 29
Northrup, W. P., intrapleural lipoma, 67, 68
Nux vomica, use of, in hyperchlorhydria, 193

Opium, use of, in myocarditis, weak heart and dilated heart, 534
Osler, W., fever in chronic endocarditis, 87
intrapleural lipoma, 66

Pancreatitis, constituent of the bile causing, 537
Peabody, G. L., intestinal perforation in typhoid fever, 338
intrapleural lipoma, 68
Pearce, R. M., arteriosclerosis, 532
experimental arteriosclerosis, 513
Perforation, intestinal, in typhoid fever, in early life, 328
Pericardial exploration, 57
Pericarditis, acute, 57
Peripheral phlebosclerosis, 525
Phlebosclerosis, peripheral, 525
Pneumococcus sepsis, 379
Pneumonia, acute non-tuberculous, 173
herpes complicating, 165
Preble, R. B., fever in chronic endocarditis, 86
President, address of, 1
Proteid diet, some considerations on, 181
Purpura hemorrhagica, case of severe, 278

Rhythmic lateral displacement of the heart as a sign of unilateral pleuritic exudate, 89
Robinson, B., some phases of the neurotic heart, 29
use of opium in myocarditis, 535
Rotch, T. W., intrapleural lipoma, 68

Salant, W., studies on the toxicity of bile, 196
Sawyer, J. P., relation of stomach disorders to diabetes mellitus, 446, 468
Sepsis, pneumococcic, 379
Septicemia, gonorrheal, and endocarditis, 391
Sippy, B. W., hematemesis from gastric ulcer, 349
remarks on the treatment of cardiospasm by new esophageal dilator, 324
Sphygmogram from two cases of bradycardia, 158
Stanton, E. MacD., experimental arteriosclerosis, 513
Stengel, A., chlorids in nephritis, 439
Sternberg, G. M., chlorids in nephritis, 443
Stewart, D. D., chronic poisoning by acetanilid, 47
concerning the obscurity of diagnosis sometimes attending stone in the kidney, 108, 140, 141
epigastric linea alba hernia as a little recognized source of abdominal pain and of gastric symptoms, 96
use of nux vomica in hyperchlorhydria, 195
Stomach disorders, relation of, to diabetes mellitus, 446
cardiospasm, use of esophageal dilator in, 324
ulcers, diagnosis and treatment of, 339
Stone in kidney, 108
Strong, R. P., study of the etiology of tropical ulcer, 383
Studies on the toxicity of bile, 196

Thacher, J. S., fever in chronic endocarditis, 70, 88
pneumococcus sepsis, 379
Thayer, W. S., gonorrheal septicemia and endocarditis, 391
lymphatic leukemia, 264
Thompson, W. G., fever in chronic endocarditis, 84
hematemesis from gastric ulcer, 339, 350
Toxicity of bile, studies on, uremia, 196
Tropical ulcer, 383
Trudeau, E. L., address of President, 1
Typhoidal perforation, 328
Tyson, J., chlorids in nephritis, 444
fever in chronic endocarditis, 86
relation of stomach disorders to diabetes mellitus, 467
stone in kidney, 140
use of nux vomica in hyperchlorhydria, 195

Ulcer, gastric, and hematemesis, 339
tropical, 383
Uremia, 237

Vaughan, V. C., a brief report on research in the writer's laboratory on bacterial toxins and immunity, 265, 277
fever in chronic endocarditis, 87
proteid diet, 191

Welch, W. H., arteriosclerosis, 532
bacterial toxins and immunity, 276
lymphatic leukemia, 264
Williams, F. H., intrapleural lipoma, 77
metabolism in leukemia, 322
Wilson, J. C., chylous and chyliform effusions into the serous sacs, 142

X-ray, influence of, in leukemia, 294
Xanthelasma and chronic jaundice, 241